Development of Catalytic Stereoselective Aldol Cyclisations

Thesis Submitted in Accordance with the Requirements of The University of Edinburgh for the degree of Doctor of Philosophy

By

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This thesis is dedicated to my parents Sandra and James

Also to my wife Eleanor

Acknowledgements

Firstly, I would like to thank Dr. Hon Wai Lam for giving me the opportunity to work in his group. Being one of his first students I would like to think I helped lay the foundations for one of the best research groups at Edinburgh University, both in terms of academic achievement and overall team spirit.

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To Euan, Ralph and Myriam, thanks for your friendship and support over the past two years. It has been a privilege working along side all of you and I hope that we can all keep in touch.

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To my parents, Sandra and Jim and my brother David for all their love and support. I would not be where I am today without their constant belief that I would achieve what ever I set my heart on. Thank you.

A massive thanks to my beautiful wife, Eleanor. This past year hasn't been the easiest for us in our marriage but I want to thank you from the bottom of my heart for everything you have done for me. You have been a fantastic support for me and constantly bring happiness into my life. I will love you always.

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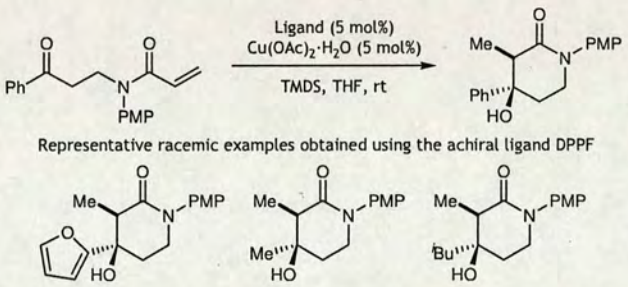
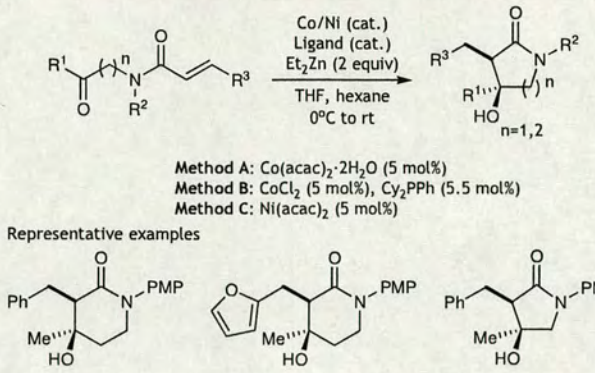


II. **Diastereoselective cobalt and nickel-catalysed reductive aldol cyclisations using diethylzinc as the stoichiometric reductant**

The development of a diastereoselective reductive aldol reaction and its application in the synthesis of substituted 4-hydroxypiperidin-2-ones and pyrrolidin-2-ones are described. The reactions proceed in the presence of either $Co(acac)_2 \cdot 2H_2O$ or $Ni(acac)_2$ and diethylzinc. The scope of this process with respect to the α,β–unsaturated component is broad, encompassing a range of aliphatic and aromatic groups. Catalyst optimisation studies including the evaluation of a number of chiral, non-racemic ligands are discussed.



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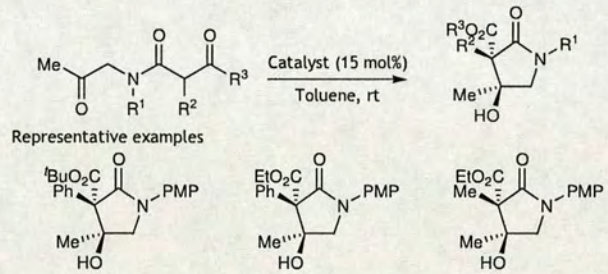


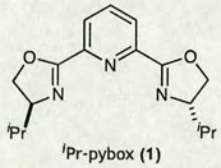
List of Abbreviations

acac	acetylacetonate
aq	aqueous
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
BIPHEP	6,6'-dimethoxybiphenyl-2,2'-diyl)-bis-diphenylphosphine
Bn	benzyl
$(Boc)_2O$	di-^{t}butyl dicarbonate
brine	saturated sodium chloride solution
Cat	catalyst
^{13}C NMR	carbon nuclear magnetic resonance spectroscopy
COD	cyclooctadiene
DCC	1,3-dicyclohexylcarbodiimide
DMAP	4-(dimethylamino)pyridine
DMF	*N,N*-dimethylforamide
DM-SEGPHOS	5,5'-bis(di(3,5-xylyl)phosphino)-4,4'-bi-1,3-benzodioxole
DMSO	dimethyl sulfoxide
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene

dr	diastereomeric ratio
DTBM-SEGPHOS	5,5'-bis(di(3,5-di-^{t}butyl-4-methoxyphenyl)phosphino)-4,4'-bi-1,3-benzodioxole
DUPHOS	1,2-bis(2,5)-diethylphospholano benzene
ee	enantiomeric excess
EtOAc	ethyl acetate
^{1}H NMR	proton nuclear magnetic resonance spectroscopy
HPLC	high-performance liquid chromatography
hrs	hours
IR	infrared spectroscopy
min	minutes
MOP	2-(diphenylphosphino-2'methoxy-1,1'-binaphthyl)
MS	molecular sieves
nd	not determined
NMDPP	neomenthyldiphenylphosphine
nr	no reaction
OMP	2-methyoxyphenyl
Phebox-*Bn*	2,6-bis(4-benzyl-2-oxazolin-2-yl)benzene
Phebox-*ip*	2,6-bis(4-isopropyl-2-oxazolin-2-yl)benzene
PMP	4-methoxyphenyl
QUINAP	1-(2-diphenylphosphino-1-naphthyl)isoquinoline
rt	room temperature

SEGPHOS	5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole
Tf	trifluoromethansufonate
THF	tetrahydrofuran
TMDS	tetramethyldisiloxane
TMS	trimethylsilyl

Ligands



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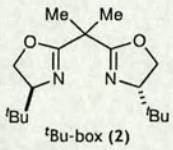

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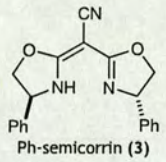
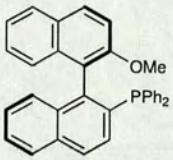


Ph-semicorrin (**3**)



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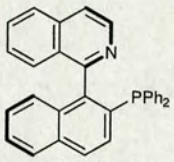

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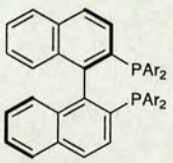

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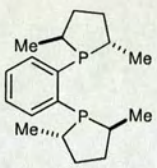

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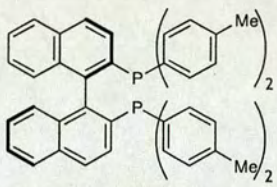

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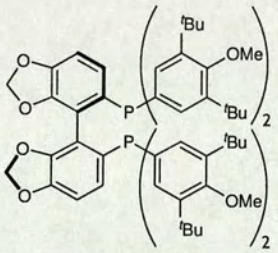

(*R*)-DTBM-SEGPHOS
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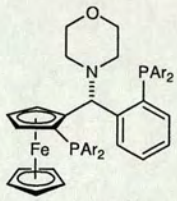
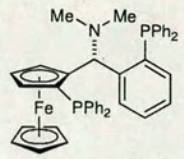


Ar = 3,5-xylyl
Taniaphos-type
22



Taniaphos-type
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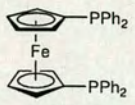

DPPF
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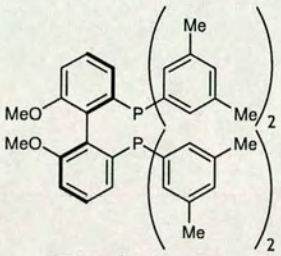
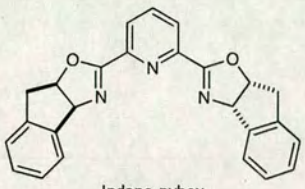


(*R*)-3,5-xylyl-MeO-BIPHEP
(26)



Indane-pybox
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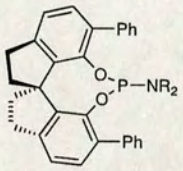

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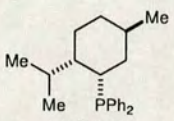
76



(+)-NMDPP
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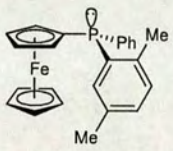

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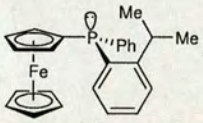

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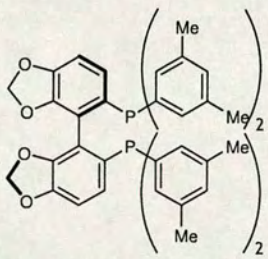
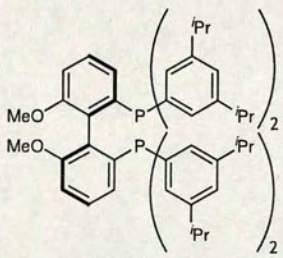
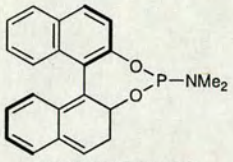


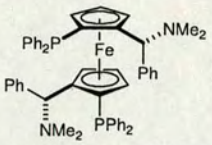
(S)-DM-SEGPHOS **(105)**



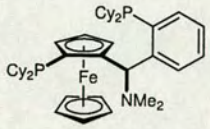
(R)-3,5-iPr-MeOBIPHEP
(106)



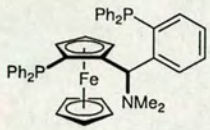
(*R*)-MONOPHOS (**107**)



(*R*)-(*S*)-NMe_2-PPh_2-MANDYPHOS (**108**)



$Cy_2PPhCHNMe_2$-T-PCy_2 (**109**)



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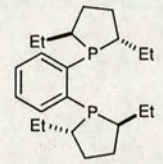
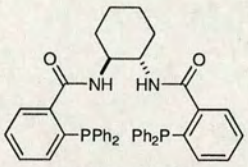
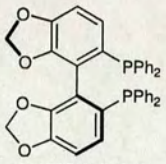


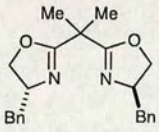
(*R*,*R*)-Et-DuPhos (**111**)



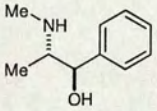
Trost ligand (**112**)



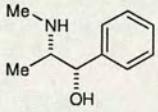
(*S*)-SEGPHOS (**141**)



Box-*Bn* (**142**)



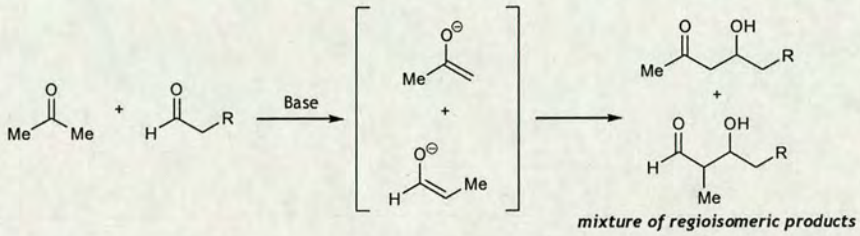
Ephedrine (**144**)



Pseudoephedrine (**145**)

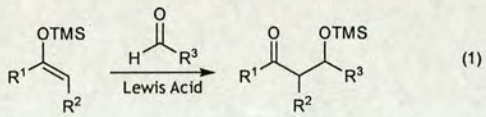
1. The Reductive Aldol Reaction

Regioselective enolate formation in the presence of multiple carbonyl groups is a particular challenge in synthetic chemistry (Scheme 1.1).



Scheme 1.1

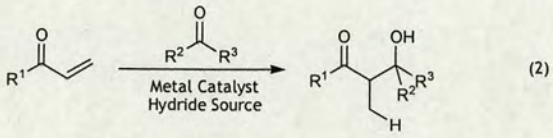
The Mukaiyama aldol reaction,[1] for example, is one possible solution to competitive enolate formation (eq 1) whereby, the latent enolate is trapped as a silyl enol ether which is then used in a subsequent coupling reaction with an aldehyde or ketone.



(1)

However, this methodology requires the pre-formation of highly reactive and relatively unstable intermediates which must be used immediately once synthesised. On the other hand, the reductive aldol reaction allows the mild and regioselective formation of the desired enolate in the presence of other carbonyl species.

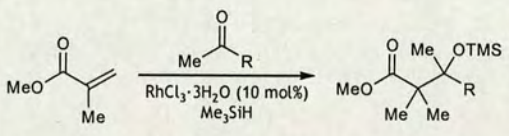
The reductive aldol reaction is the coupling of the α-carbon of an α,β-unsaturated carbonyl species to an acceptor aldehyde or ketone in the presence of a substoichiometric amount of a metal promoter and a stoichiometric amount of a reducing agent (eq 2). The β-hydroxy carbonyl products can be isolated either as the free hydroxyl compound or as the silyl ether if silanes are used as the reducing agent. In addition, the reductive aldol reaction can be carried out under mild conditions using commercially available materials with no pre-formation of an enolate required.



(2)

1.1. Rhodium-catalysed intermolecular reductive aldol reactions

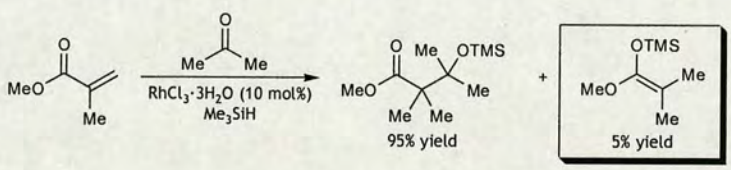
The reductive aldol reaction has attracted a great deal of attention from some of world's largest research groups since its discovery in the late 1980's. This methodology was pioneered by Revis and Hilty who in 1987 demonstrated that a selection of ketones and aldehydes could be efficiently coupled to a variety of acrylates in the presence of $RhCl_3 \cdot 3H_2O$ and trimethylsilane (Table 1.1).[2]



R	%Yield
Me	95
Et	91
H	78
OEt	nr

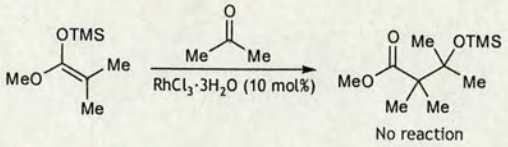
Table 1.1

In their work Revis and Hilty observed a small amount of silyl ketene acetal as a side-product (eq 3).



(3)

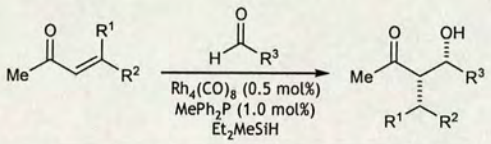
They postulated that the rhodium catalyst promoted the formation of the silyl ketene acetal by the oxidative addition of the silane followed by acrylate insertion and reductive elimination. This acetal would then be free to couple with the electrophile in a Mukaiyama type coupling (eq 4). However, when the silylketene acetal was independently synthesised and subjected to the reaction conditions, no coupling between the acetal and electrophile was observed.



(4)

As a consequence, Revis surmised that the reductive aldol reaction was proceeding through a novel reaction mechanism. However, Revis was not successful in generating the products with any degree of diastereoselection.

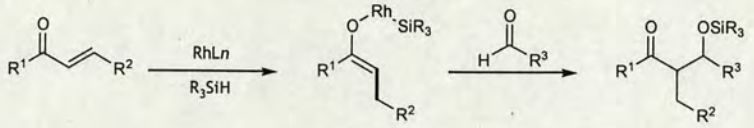
Several years after this seminal work by Revis and Hilty, Matsuda and co-workers reported the first example of a diastereoselective reductive aldol reaction (Table 1.2).[3] Using aR $h_4(CO)_{12}$ catalyst and PPh_2Me as ligand, Matsuda illustrated that various enones could be coupled to a small selection of aldehydes in the presence of Et_2MeSiH with modest diastereoselectivities of up to 4:1 in favour of the *syn* diastereomer.



R^1	R^2	R^3	%Yield	*syn:anti*
H	Me	Ph	99	83:17
H	Me	$CH_3(CH_2)_6$	80	68:32
H	Me	c-C_6H_{11}	63	58:42
H	Ph	Ph	88	55:45
Me	Me	Ph	86	80:20

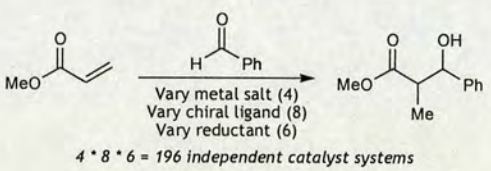
Table 1.2

In a similar fashion to Revis, Matsuda demonstrated that independently synthesised silylketene acetals were unreactive under the reaction conditions. Following mechanistic information discovered by Bergman and Heathcock in 1989,[4] Matsuda postulated a tentative mechanistic rationale for the rhodium catalysed reductive aldol reaction, where an oxygen-bound rhodium enolate reacted directly with the aldehyde (Scheme 1.2).



Scheme 1.2

More recently, the group of Morken utilised high-throughput technology to rapidly develop a catalyst system for the diastereoselective reductive coupling of acrylates with aldehydes. By using a 96-well plate, Morken and co-workers were able to analyse and compare the efficiencies of 192 independent catalyst systems for the reductive aldol reaction between methyl acrylate and benzaldehyde (Table 1.3).[5] From these results, a number of interesting observations on reaction conditions and yield were made. Firstly, the use of catechol borane as the stoichiometric reductant tends to give reactions with the majority of catalysts, whereas, trichlorosilane is only effective when $[(allyl)PdCl]_2$ is used in the presence of MOP ligand **(4)**. Additionally, it was noted that the reaction characteristics are highly sensitive to the choice of ligand and silane.



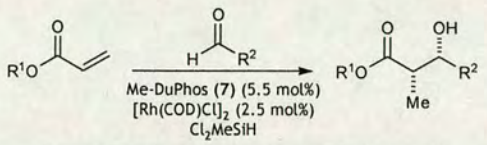
*4 * 8 * 6 = 196 independent catalyst systems*

Metal salt	Chiral ligand	Reductant
$Co(acac)_2$	^{i}Pr-pybox **(1)**	Cl_2MeSiH
$[(allyl)PdCl]_2$	^{t}Bu-box **(2)**	Et_2MeSiH
$[(COD)IrCl]_2$	Ph-semicorrin **(3)**	$PhSiH_3$
$[(COD)RhCl]_2$	MOP **(4)**	Ph_2SiH_2
	BINAP **(5)**	Cl_3SiH
	QUINAP **(6)**	catechol borane
	Me-DuPhos **(7)**	

Table 1.3

Of the catalyst systems examined, Morken opted for the combination of $[Rh(COD)Cl]_2$ with Me-DuPhos **(7)** as the ligand and dichloromethylsilane as the stoichiometric reductant (Table 1.4). Using this system, acrylates were shown to undergo reductive aldol coupling with a variety of aromatic and aliphatic aldehydes, producing the aldolate products in moderate to good yields with diastereoselectivities

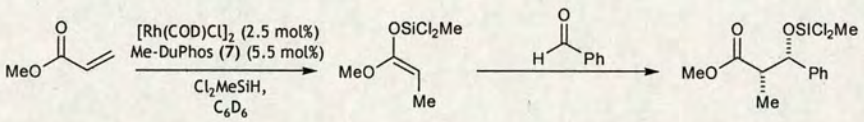
up to 23:1 (*syn*:*anti*). However, little or no enantioselectivities were observed with this catalyst system.



R^1	R^2	%Yield	*syn*:*anti*	%ee *syn*
Me	Ph	69	23:1	0
Et	1-naphth	82	10:1	0
Et	^{t}Bu	38	21:1	0
Et	^{i}Pr	15	15:1	0
Et	PhCH=CH	41	>20:1	0

Table 1.4

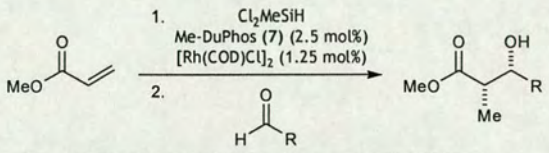
In an effort to understand the reaction pathway, Morken used NMR spectroscopy to study the generation and reactivity of reaction intermediates.[6] Initially, the Rh-DuPhos-catalysed reaction between methyl acrylate and dichloromethylsilane was shown to produce a single stereoisomer of the intermediate silylketene acetal. Introduction of benzaldehyde led to rapid consumption of the silylketene acetal forming a single diastereomer of the reductive aldol product (Scheme 1.3).



Scheme 1.3

In addition, itwas shown that vacuum-distilled silylketene acetal reacted with benzaldehyde in the absence of catalyst to provide the aldol adduct with high levels of stereoselection. It was concluded that the role of the Rh-DuPhos complex in the reductive aldol reaction is to catalyse the formation of the silylketene acetal and that the chiral catalyst is not involved in the aldol addition step. As a consequence, these results would seem to preclude the prospect of an enantioselective variant of this system. Nevertheless, this system represents a method of generating *syn* aldol

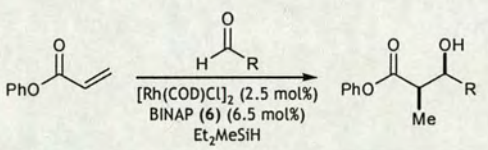
adducts with a large variety of aldehydes in excellent yields and selectivities superior to the previously mentioned single-sequence procedure (Table 1.5).[5]



R	%Yield	*syn:anti*
PhCHO	94	>60:1
PhCH=CHCHO	95	13:1
^{i}PrCHO	89	9:1
EtO_2CCHO	84	>20:1
$BnOCH_2CHO$	80	>20:1

Table 1.5

On the other hand, by modifying the catalyst system to incorporate excess (*R*)-BINAP **(6)**as ligand and Et_2MeSiH as the reductant, Morken was able to effect the reductive aldol reaction between acrylate esters and aldehydes to give the products with impressive levels of enantioselection. Indeed, this work constitutes the first reported example of a catalytic asymmetric reductive aldol reaction (Table 1.6).[7]



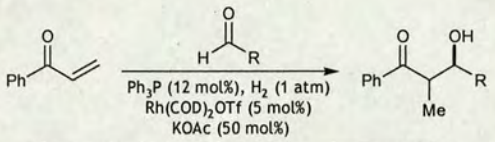
R	%Yield	*syn:anti*	%ee *syn(anti)*
Ph	72	3.4:1	87(34)
Et	59	5.1:1	88(7)
c-C_6H_{11}	54	3.9:1	84(48)
^{t}Bu	48	1.8:1	45(>99)
1-naphth	82	3.8:1	80(13)
PhCH=CH	0	-	-

Table 1.6

He surmised that during the initial catalyst screening process equimolar quantities of ligand and metal salt resulted in incomplete complexation, resulting in very low enantioselection. However, by adding excess ligand with respect to the metal salt,

increased complexation resulted in increased enantioselectivity to a maximum of 88% albeit with a greatly reduced diastereoselection of up to 5:1 (*syn*:*anti*)f rom the initial 23:1 (Table 1.4).

Krische further extended the scope of the rhodium catalysed reductive aldol reaction by employing elemental hydrogen as the stoichiometric reductant (Table 1.7).[8] A variety of aromatic aldehydes could be efficiently coupled with phenyl vinyl ketone in the presence of $Rh(COD)_2OTf$, PPh_3, KOAc and hydrogen gas (1 atm) at room temperature to give the reductive aldol adducts in good yields but with only poor levels of diastereoselection of up to 2.5:1 (*syn*:*anti*).



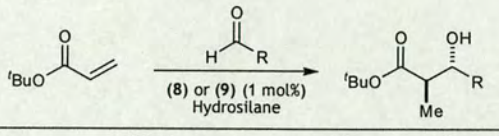
R	%Yield	*syn*:*anti*
4-NO_2PhCHO	92	1.8:1
4-MeOPhCHO	75	1.7:1
2-furylCHO	88	2.5:1
2-naphth	61	2.3:1
4-FPh	65	2:1
$CH_3(CH_2)_2$	44	2:1

Table 1.7

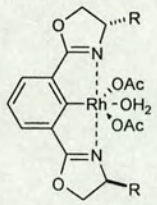
It was found that competitive conjugate reduction of phenyl vinyl ketone was a prevalent side-reaction. However, by increasing the molar equivalents of phenyl vinyl ketone and reducing the catalyst loading of rhodium salt from 10 mol% to 5 mol% the yield of aldol adducts could be maximised.

Initial work by Nishiyama and co-workers into the rhodium-catalysed asymmetric conjugate reduction of α,β-unsaturated esters identified a rhodium complex with chiral C2-symmetric N-C-N (Phebox) ligands **(8)** and **(9)** in combination with a variety of silanes as a highly efficient catalyst system.[9] Application of this system to the reductive coupling of *tert*-butyl acrylate with a diverse selection of aromatic

aldehydes provided the aldol adducts in excellent yields with remarkable levels of *anti*-diastereoselectivity and enantioselectivity (Table 1.8).



R	%Yield	*syn*:*anti*	%ee *anti*(*syn*)
4-MeOPh	98	6:94	94(42)
2-Naphthyl	93	7:93	96(5)
PhCH=CH	56	19:81	93(79)
$PhCH_2OCH_2$	56	19:81	93(79)
c-C_6H_{11}	70	13:87	93(12)
4-CF_3Ph	93	8:92	89(34)



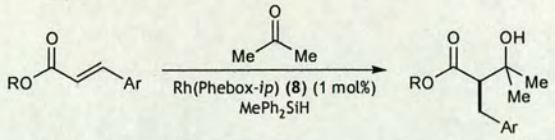
R = ^{i}Pr: Rh(Phebox-*ip*) **(8)**

R = Bn: Rh(Phebox-*bn*) **(9)**

Table 1.8

Notably, this catalyst system tolerates a large variety of silane reductants. Alkoxy, alkyl and aromatic silanes can be used with no loss in yield, diastereoselectivity or enantioselectivity. Indeed the robust nature of this methodology and remarkable levels of *anti* selectivity represent a complete contrast to the methodologies developed by Morken and Krische (*vide supra*).

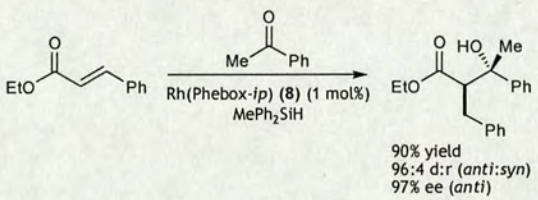
Nishiyama extended this strategy to encompass the reductive coupling of cinnamates with acetone in the presence of RhPhebox-*ip* **(8)** and $MePh_2SiH$ (Table 1.9).[10]



R	Ar	%Yield	%ee
Me	Ph	83	96
^{i}Pr	Ph	82	98
Bn	Ph	82	96
^{t}Bu	Ph	36	97
Ph	Ph	28	<1
Et	CF_3	64	97
Et	Cl	62	97
Et	OMe	81	96

Table 1.9

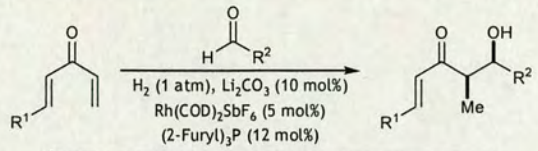
The aldol products were produced in moderate to excellent yields and with enantioselectivities of up to 98%. By replacing acetone with an unsymmetrical ketone such as acetophenone the corresponding aldol adduct could be isolated in 90% yield with a diastereoselectivity of 96:4 (*anti*:*syn*) and an enantioselectivity of 97% (eq 5).



(5)

However, replacement of the cinnamate with the corresponding acrylate led to diminished yields and selectivities.

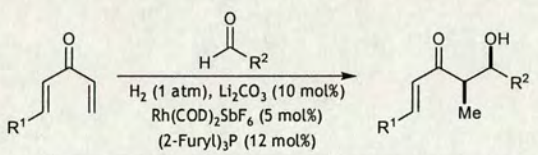
Recently, Krische and co-workers have developed methodology to increase the substrate diversity in order to improve the chemical utility of the reductive products. It has been reported that the reductive coupling of divinyl ketones to a diverse range of aldehydes has been accomplished using cationic rhodium catalysts ligated by tri-2-furyl phosphine in the presence of elemental hydrogen (Table 1.10).[11]



R^1	R^2	%Yield	*syn:anti*
Me	4-NO_2Ph	82	13:1
Me	$BnOCH_2$	80	9:1
Me	2-NO_2PhCH=CH	75	12:1
4-NO_2Ph	4-NO_2Ph	93	10:1
4-NO_2Ph	$BnOCH_2$	90	10:1
4-NO_2Ph	2-NO_2PhCH=CH	71	13:1

Table 1.10

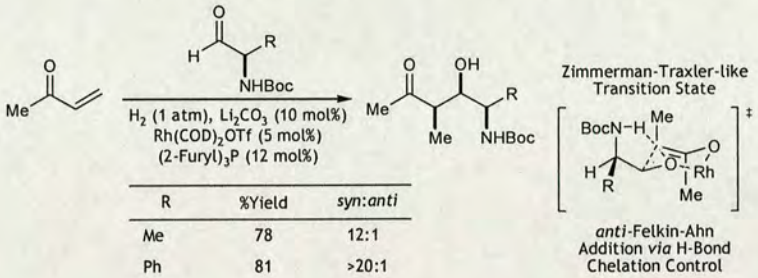
By careful choice of anionic counterion, the system could be optimised to allow the efficient coupling of the less substituted vinyl moiety to the aldehydes in good yield and with excellent *syn* diastereoselection. Furthermore, the yield of the reductive aldol addition of styryl vinyl ketones to aromatic aldehydes is dependent on the electron releasing properties of the aromatic *para*-substituent of the styryl unit (Table 1.11). Electron donating substituents, for example, dimethylamino led to increased product yield over electron withdrawing substituents like nitro. This trend can be attributed to the modulation of the HOMO in the rhodium enolate, where by the more reactive intermediates are derived from styryl vinyl ketones with electron donating *para*-substituents.



R^1	R^2	%Yield	*syn:anti*
4-NO_2Ph	4-NO_2Ph	44	16:1
Ph	4-NO_2Ph	50	12:1
4-MeOPh	4-NO_2Ph	64	11:1
4-(Me_2N)Ph	4-NO_2Ph	93	10:1

Table 1.11

A further advancement from the Krische group has been the development of a hydrogen mediated reductive aldol coupling of vinyl ketones to enriched α-chiral aminoaldehydes (Table 1.12).[12] Incorporation of an internal hydrogen bond donor was observed to be essential for controlling selectivity as well as enhancing the reactivity of the aldehyde.



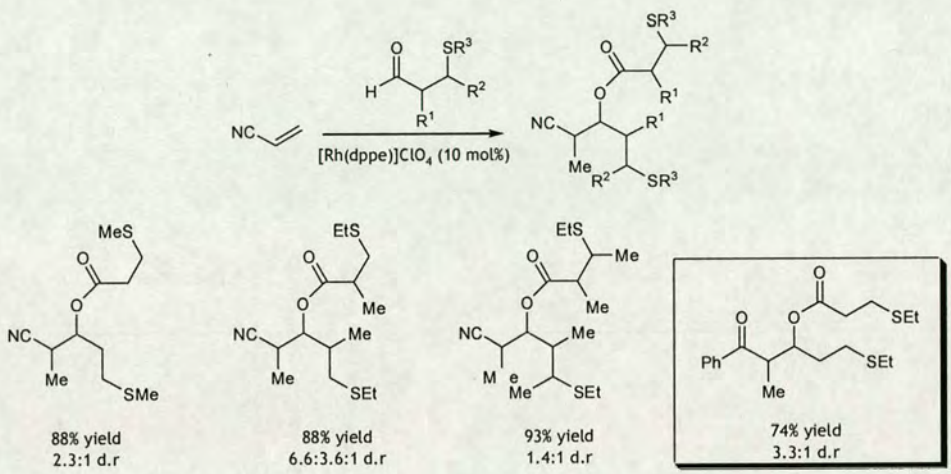
R	%Yield	*syn*:*anti*
Me	78	12:1
Ph	81	>20:1
^{i}Pr	55	10:1
CH_2Ph	84	>20:1

Table 1.12

The *syn*-aldol, *anti*-Felkin-Ahn selectivity can be accounted for by invoking a Zimmerman-Traxler[13] transition state involving hydrogen-bond control for the substrates containing a free N-H bond. Aldehydes derived from amino acids incorporating either aromatic or aliphatic side-chains undergo reductive aldol coupling to give the *syn*-aldol products in excellent yield with diastereoselectivities of up to ≥20:1. The introduction of an additional hydrogen bond donor in the form of *tert*-amyl alcohol leads to an erosion in the diastereoselectivity, providing further evidence to support asymmetric induction through intramolecular hydrogen bonding.

To date, the majority of rhodium-catalysed intermolecular reductive aldol reactions incorporate stoichiometric quantities of silanes or molecular hydrogen as the reductant. Despite the obvious merits of these systems there are some remaining limitations to their usefulness. For example, reaction efficiency can be reduced by competing reaction pathways such as C=O and C=C bond reduction and the formation of silyl enol ethers. In effort to avoid these limitations Willis and co-workers reported a novel rhodium-catalysed reductive aldol system where β-methyl

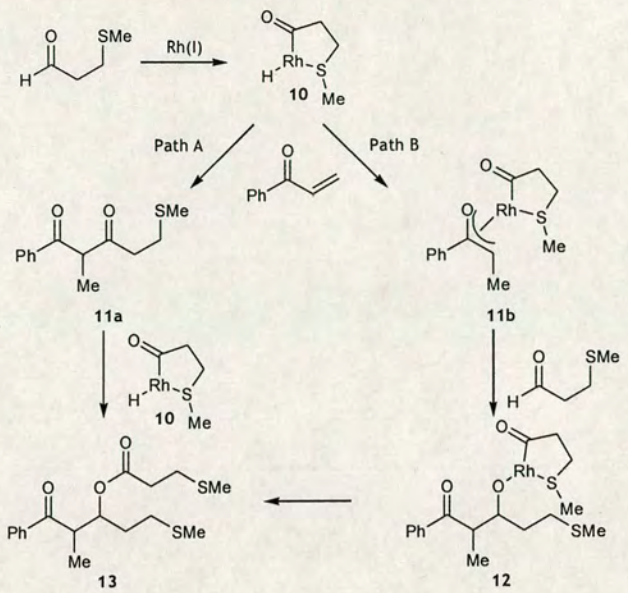
sulfide-substituted aldehydes act both as the substrate and the reductant (Scheme 1.4).[14]



Scheme 1.4

A diverse variety of β-methyl sulfide-substituted aldehydes are tolerated in the reductive coupling with acrylonitrile. The reaction also tolerates variations in the α,β -unsaturated carbonyl species as acrylonitrile can be readily exchanged for phenyl vinyl ketone and phenyl acrylate with no loss in reactivity. In general, the reductive aldol adducts are generated in yields approaching 93% albeit with poor levels of diastereoselection.

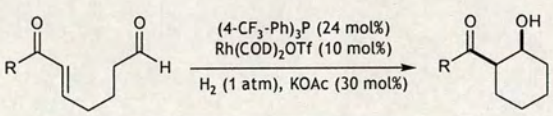
Two mechanisms are proposed in the report with both being initiated by the oxidative insertion of aRh(I) species into the aldehyde C-H bond generating the chelated acyl rhodium hydride species **10**. Path A then involves the hydroacylation of phenyl vinyl ketone to generate the ketone **11a** followed by the Tischenko-type[15] reduction of the ketone with another molecule of acyl rhodium hydride generating the product **13**. Path B involves conjugate addition of the rhodium hydride species onto phenyl vinyl ketone. The intermediate rhodium enolate **11b** then reacts with the starting aldehyde to generate the aldol adduct **12**. Regeneration of the active catalyst species and liberation of the product **13** occurs following the reductive elimination of the rhodium species (Scheme 1.5).



Scheme 1.5

1.2. Rhodium-catalysed intramolecular reductive aldol reactions

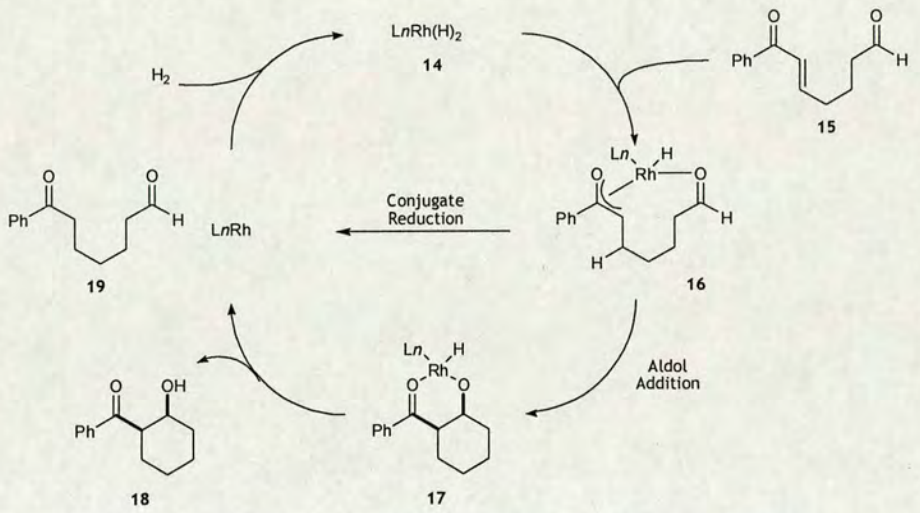
The first example of a rhodium-catalysed intramolecular reductive aldol reaction was reported by Krische and co-workers in 2002. It was shown that under hydrogenative conditions, aldehydes tethered to enones *via* an all carbon linkage underwent efficient reductive aldol cyclisation giving the desired six membered carbocycles (Table 1.13).[8]



R	%Yield	*syn:anti*
Ph	89	10:1
4-MeOPh	74	5:1
2-furyl	70	6:1
2-naphthyl	90	10:1
2-thiophenyl	76	19:1
Me	65	1:5

Table 1.13

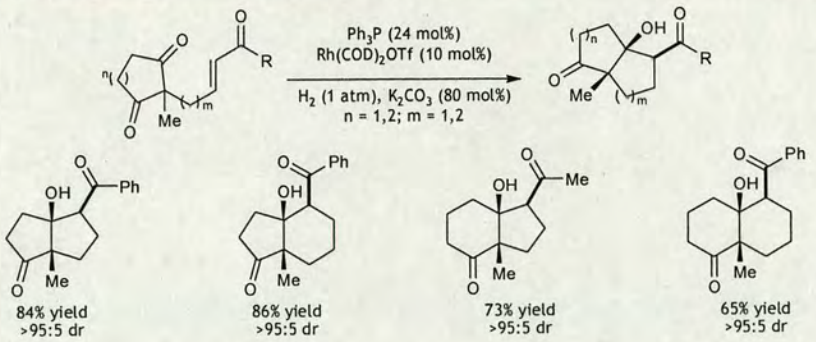
Initially, competitive conjugate reduction of the enone led to attenuated yields of the desired cyclised product. However, through a combination of modulating the ligand electronic effects and the use of potassium acetate as an additive, the levels of conjugate reduction could be minimised. Using the optimised conditions, a number of aromatic, heteroaromatic and alkyl enones perform well in the reductive cyclisation to give the products in yields of up to 90% and with diastereoselectivities ranging between 5:1 and 19:1. Moreover, Krische reported a plausible catalytic cycle for this process (Scheme 1.6).



Scheme 1.6

Oxidative addition of L*n*Rh(I) into elemental hydrogen produces rhodium hydride species **14**. This is followed by hydrometallation of enone **15** to give rhodium enolate **16**. Aldol addition to the internal aldehyde moiety gives rhodium aldolate **17**. Finally, an oxygen-hydrogen reductive elimination releasesthe product **18** and the catalyst L*n*Rh(I). However, a competing reaction pathway exists which involves the conjugate reduction of rhodium enolate **16** to furnish the reduced by-product **19**.

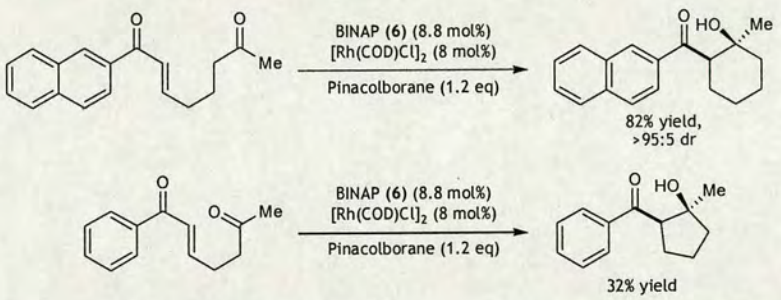
This work was later extended in a follow-up paper in which ketones were employed as the internal electrophile allowing the construction of a variety of five- and six-membered carbocycles (Scheme 1.7).[16]



Scheme 1.7

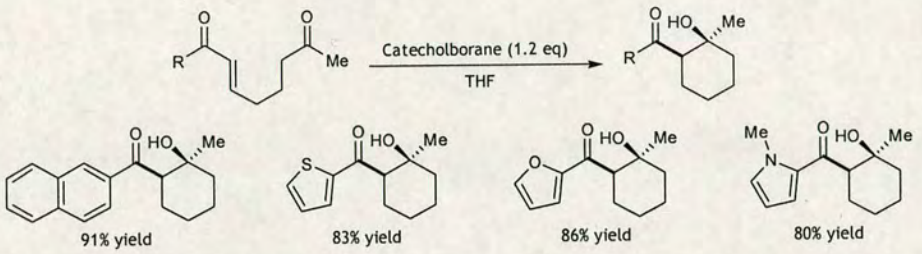
Through the use of diketone electrophiles, products containing three stereogenic centres, two of which are contiguous quaternary stereocentres could be synthesised in excellent yields and with remarkable control of the relative stereochemistry (d.r. >95:5). These levels of diastereoselection were consistent for all cyclisations reported.

In addition to this methodology, alternative reductants were investigated by Krische.[17] To this end a combination of $[Rh(COD)Cl]_2$ and borane reductants such as pinacolborane proved to be effective in the reductive aldol cyclisation of enones tethered to ketones through an all carbon linkage (eq 6 and 7). Six-membered rings are readily formed in high yields as single diastereomers (eq 6); however, under the same conditions, the formation five-membered rings proved to be inefficient (eq 7).



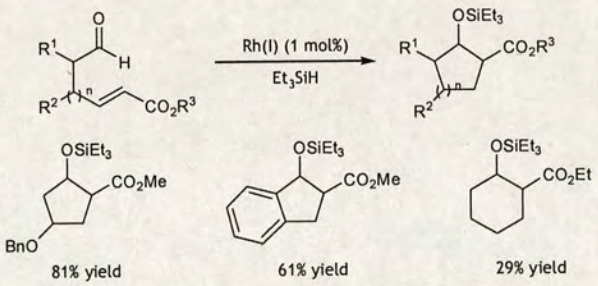
Alternatively, catecholborane was shown to efficiently mediate the reductive aldol cyclisation of enones tethered to ketones through an all carbon linkage. Using stoichiometric quantities of catecholborane, Krische demonstrated that a variety of

six-membered carbocycles could be readily synthesised in excellent yields as a single diastereomer (Scheme 1.8).[17]



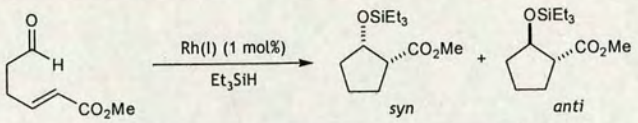
Scheme 1.8

In asim ilar fashion to Krische, Motherwell has also reported the reductive aldol cyclisation of aldehydes tethered to enones *via* an all-carbon linkage to produce a selection of five- and six-membered carbocycles (Scheme 1.9).[18]



Scheme 1.9

The combination of substoichiometric quantities of a rhodium salt and triethylsilane allows the product to be obtained in up to 81% yield and with a diastereoselectivity of up to 3.3:1. Motherwell observed that olefin geometry did not influence the stereochemical outcome of the cyclisation, with both (*E*)an d (*Z*)isom ers giving the same product distribution. However, the nature of the rhodium catalyst has a dramatic effect of the diastereoselectivity of the process (Table 1.14).



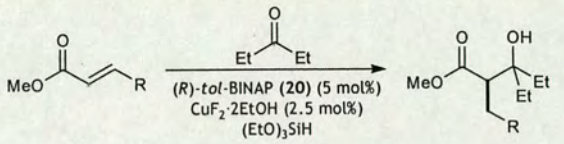
Catalyst	%Yield	*syn:anti*
$RhCl(PPh_3)_3$	76	3:1
$[RhCl(COD)_2]_2$ - DIPHOS	78	3.3:1
$RhH(PPh_3)_4$	81	1:2

Table 1.14

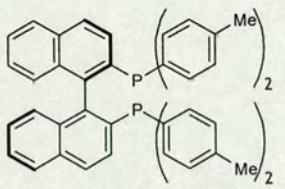
The use of Wilkinson's catalyst $RhCl(PPh_3)_3$ gives the silylated cyclopentanol product in 76% yield in favour of the *syn* diastereomer (3:1), whereas the use of the hydridotetrakis (triphenylphosphine) rhodium(I) salt $RhH(PPh_3)_4$ not only proves to be the most active catalyst but also leads to a reversal of selectivity with predominant formation of the *anti* diastereomer (1:2).

1.3. Copper-catalysed intermolecular reductive aldol reactions

Copper salts have been used to great effect in the enantioselective conjugate reduction of various α,β-unsaturated carbonyl compounds since 1999.[19] Despite this the use of copper salts in reductive aldol chemistry has only recently been explored. To this end, the first example of an enantioselective copper catalysed intermolecular reductive aldol reaction was reported by Shibasaki and co-workers in 2006. Optimised conditions include a combination of $CuF_2{\cdot}3PPh_3$ and a chiral non-racemic ligand such as (*R*)-tol-BINAP **(20)** in the presence of $(EtO)_3SiH$ as the stoichiometric reductant. Using these conditions, substituted methyl acrylates couple with symmetrical ketones to give the corresponding aldol adducts in good yield and with moderate to good levels of enantioselection (Table 1.15).[20]



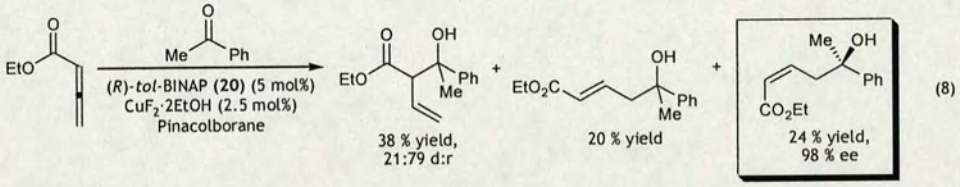
R	%Yield	% ee
Me	93	71
Et	96	76
Ph	52	80



(*R*)-*tol*-BINAP (**20**)

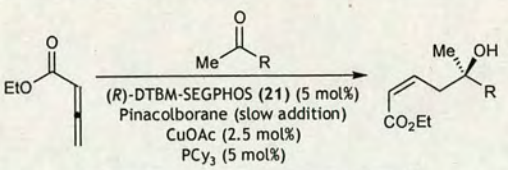
Table 1.15

Allenic esters were further shown to be potent nucleophiles, giving a mixture of aldol products (eq 8).[20]

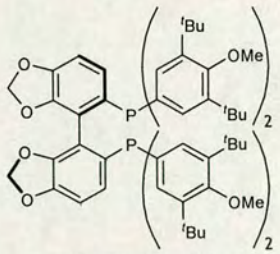


(8)

Interestingly, the aldol products were formed in low to moderate yields but with excellent levels of enantioselection when pinacolborane was used as the reductant. In addition, Shibasaki further explored the effect of copper salt and ligand additive on the enantioselectivity of the asymmetric reductive aldol addition of allenic esters to ketones.[21] A combination of pinacolborane as the stoichiometric reductant and (*R*)-DTBM-SEGPHOS **(21)** as the chiral non-racemic ligand were chosen and a variety of copper(I) salts and mono-phosphine additives were screened for efficiency. Consequently it was found that the use of CuOAc and PCy_3 proved to be an extremely effective combination for a large variety of ketones, giving predominately the γ-*cis*-selective reductive aldol adducts in excellent yields and with excellent levels of enantioselection (Table 1.16).



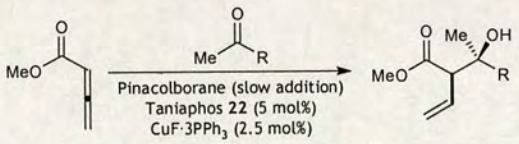
R	%Yield	%ee
Ph	96	99
4-ClPh	93	98
PhCH=CH	97	84
^{i}Pr	80	98



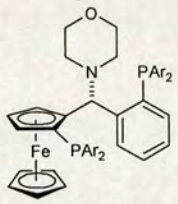
(*R*)-DTBM-SEGPHOS
(21)

Table 1.16

The α-selective aldol adducts could also be obtained by further changes to the catalyst system. By using CuF·3PPh$_3$ as the catalyst in combination with TaniaPhos-type ligand **22**, the α-selective aldol products are generated in high yields, with moderate diastereoselectivity and with high levels of asymmetric induction for a large variety of ketones (Table 1.17).



R	%Yield	*syn*:*anti*	%ee
Ph	90	10:1	84
4-ClPh	89	8:1	83
PhCH=CH	87	9:1	67
4-IPh	86	7:1	84



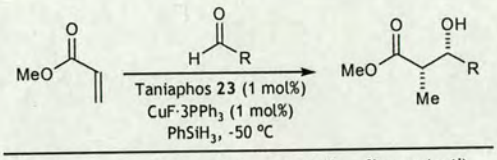
Ar = 3,5-xylyl
Taniaphos-type
22

Table 1.17

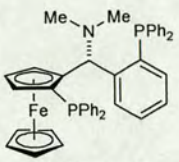
This powerful methodology developed by Shibasaki and co-workers allows the selective formation of enantiomerically enriched α-linked or γ-linked aldol adducts by simply changing the metal/ligand combination.

Independently from Shibaski, Riant and co-workers also reported the copper catalysed reductive aldol reaction of methyl acrylate with a variety of aldehydes.[22] Using a combination of [CuF(PPh$_3$)$_3$], bisphosphine ligand and PhSiH$_3$ as the

stoichiometric reductant the reductive aldol products could be obtained in excellent yields and with high levels of asymmetric induction when Taniaphos-type ligands, such as **23** are used (Table 1.18).



R	%Conversion	*syn:anti*	%ee *syn(anti)*
^{i}Pr	99	64:36	73(26)
Ph	99	41:58	nd(72)
4-ClPh	99	44:56	85(69)
4-MeOPh	99	60:40	68(72)



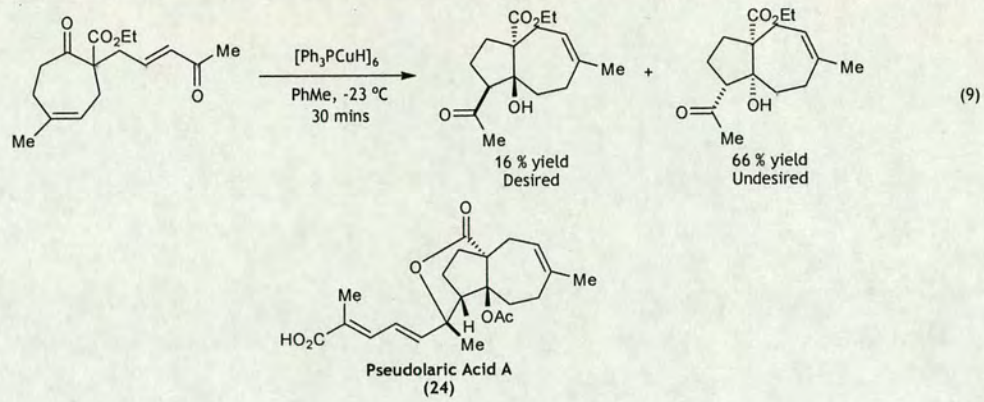
Taniaphos-type
23

Table 1.18

Although the catalyst system was noted to be highly active with a turnover frequency (TOF) estimated at 40,000 h^{-1} the levels of diastereoselection were poor in the majority of cases. The poor levels of diastereoselection maybe improved for a selection of aldehyde electrophiles when the reactions are allowed to run at -50 °C.

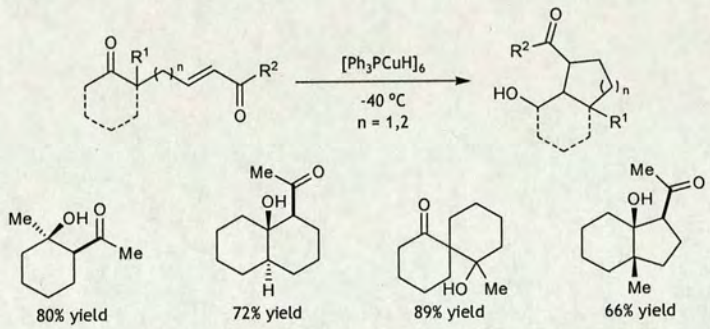
1.4. Copper-mediated intramolecular reductive aldol reactions

The first example of a copper mediated intramolecular reductive aldol reaction was reported by Chiu and co-workers in 1998, during her studies towards the total synthesis of *pseudolaric acid A* **(24)** (eq 9).[23] The key step in the synthesis involves the use of a stoichiometric amount of Stryker's reagent ($[Ph_3PCuH]_6$) at low temperature to promote the reductive aldol cyclisation. The desired 5,7-bicyclic ring system is produced in a yield of 66% and with a diastereoselectivity of 3:1. However, the major diastereomer was later confirmed by X-ray crystallography to be the undesired *cis*-fused ring system.



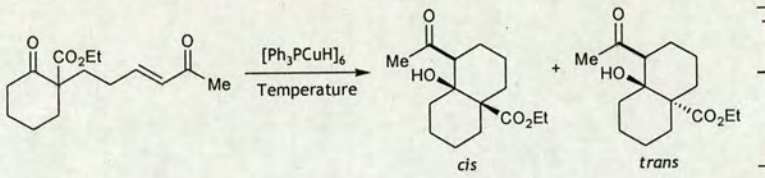
(9)

By further extending the scope of this methodology, Chiu and co-workers were able to demonstrate that a number of five- and six-membered carbocycles could be formed in one-pot with diastereoselectivities of up to 95:5 in the majority of cases (Scheme 1.10).[24]



Scheme 1.10

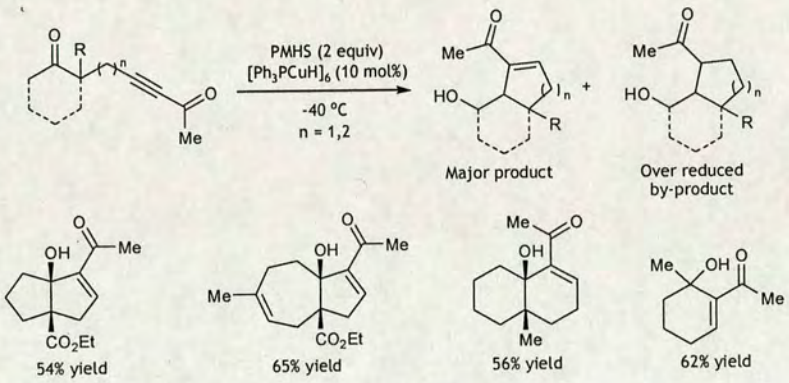
In addition, it was shown that the reaction temperature is critical in controlling the diastereoselectivity and yield of cyclisations where fused ring systems are formed (Table 1.19). At temperatures of -10 °C a mixture of *cis*- and *trans*-fused ring systems are formed with the more thermodynamically stable *trans*-product dominating. However, on cooling to -40 °C the *cis*-fused kinetic product could be exclusively obtained in 93% yield.



T(°C)	t(h)	%Yield	
		cis	*trans*
-40	1	93	0
-25	0.5	79	3
-10	0.25	12	58

Table 1.19

Subsequently, Chiu and co-workers improved upon this methodology by developing a catalytic variant, which uses polymethylhydrosiloxane (PMHS) as the stoichiometric reductant in the presence of a substoichiometric amount of Stryker's reagent (Scheme 1.11).[25]

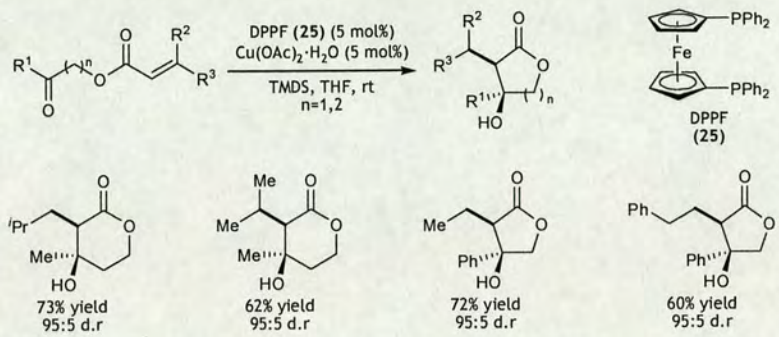


Scheme 1.11

A number of diketone substrates efficiently cyclised to give the products in moderate to good yields and with very high diastereoselectivities. In the case of bicycle formation the *cis*-fused ring systems were the sole or major product in all systems examined. Side-product formation due to over-reduction occurs with the majority of substrates and accounts for 6-39% of the mass balance. Nevertheless this methodology represents the first example of a non-radical based copper-catalysed reductive aldol reaction.[26]

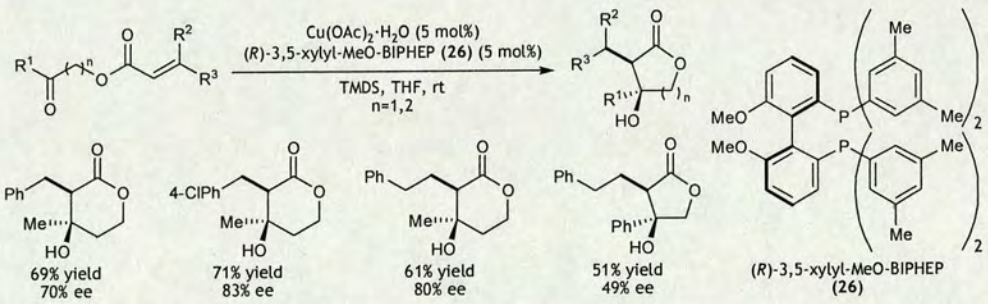
The scope of the intramolecular copper-catalysed reductive aldol methodology was extended by Lam and co-workers to the synthesis of five- and six-membered β-

hydroxylactones.[27] Using a combination of $Cu(OAc)_2 \cdot H_2O$, DPPF **(25)** and tetramethyldihydrosiloxane (TMDS) as the stoichiometric reductant, various α,β-unsaturated carbonyl compounds tethered to ketones through an ester linkage underwent reductive aldol cyclisation to provide the reductive aldol products in moderate yield and with excellent levels of diastereoselectivity (Scheme 1.12).



Scheme 1.12

Moreover, the process could be rendered enantioselective by the replacement of **(25)** with an appropriate chiral, non-racemic bis-phosphine ligand. Consequently, a variety of five- and six-membered β-hydroxylactones could be obtained with enantioselectivities of up to 83% (Scheme 1.13).



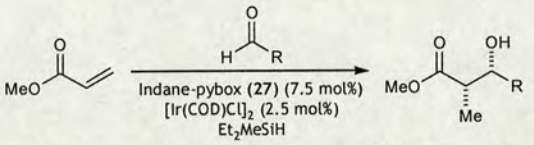
Scheme 1.13

This process developed by Lam and co-workers was the first reported example of the formation of heterocyclic ring systems *via* a reductive aldol methodology and to date

is the only example of an enantioselective copper-catalysed intramolecular reductive aldol reaction.

1.5. *Iridium-catalysed intermolecular reductive aldol reactions*

An additional interesting result from Morken's high throughput screening of catalyst systems was that a combination of $[Ir(COD)Cl]_2$ and Indane-pybox **(27)** was able to effect the enantioselective reductive aldol reaction. This metal-ligand combination appeared very attractive due to the ease of which these ligands maybe accessed from commercially available materials. To this end a variety of pybox ligands were investigated and found to catalyse the reductive aldol reaction of methyl acrylate with various aldehydes (Table 1.20).[28]



R	%Yield	*syn:anti*	%ee *syn*
Ph	68	6.6:1	94
$BnOCH_2$	49	9.9:1	96
$TBSOCH_2$	47	8.2:1	96
$BnO(CH_2)_2$	65	2.7:1	82
Et	<5	-	-
PhCH=CH	nr	-	-

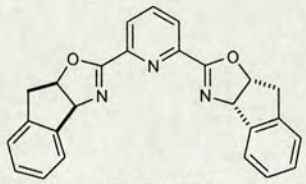
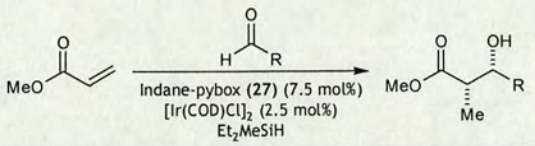


Table 1.20

It was found that bulkier pybox-type ligands gave the reductive aldol products with greater levels of enantioselection; however, changing the steric bulk had little effect on the diastereoselectivity. Aromatic and α-hydroxy aldehydes are the most reactive electrophilic coupling partners whereas simple aliphatic aldehydes prove to be relatively unreactive. Moreover, it was reported that pre-existing substrate chirality had a dramatic effect on the selectivity on the reaction. Reductive aldol coupling with aldehydes bearing a β-hydroxy substituent gave the corresponding aldol products in moderate yields and with excellent selectivity, regardless of which enantiomer of aldehyde was employed. Conversely, aldehydes bearing an α-hydroxy

substituent led to significant double stereo-differentiation corresponding to good Felkin control (see appendix 1) in the matched substrate enantiomer (Table 1.21).



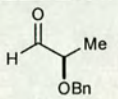
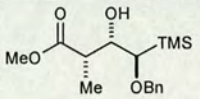
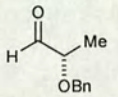
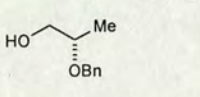
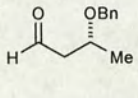
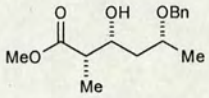
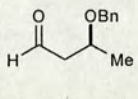
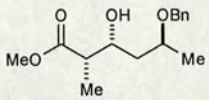
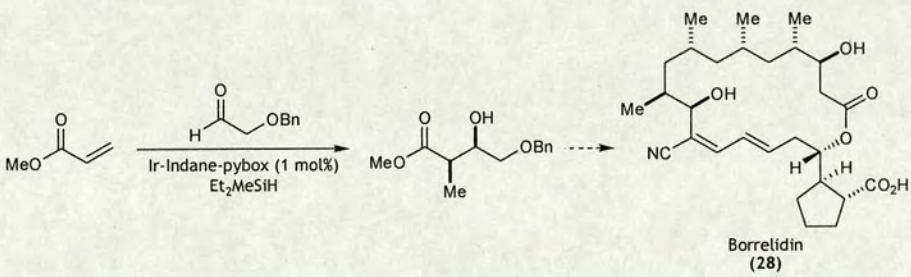
Aldehyde	Product	%Yield	*syn:anti*
		50	>95:5
		<5	-
		65	89:11
		57	88:12

Table 1.21

Morken further demonstrated the usefulness of his catalyst system when he used an iridium-indane-pybox catalysed reductive aldol reaction in the first step of the enantioselective total synthesis of Borrelidin **(28)** (eq 10).[29]

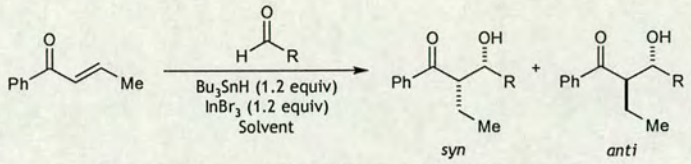


(10)

1.6. *Indium-mediated intermolecular reductive aldol reactions*

The use of indium salts in the reductive aldol reaction has been pioneered by Akio Baba and co-workers.[30] Following his work into the reduction of aldehydes and acid

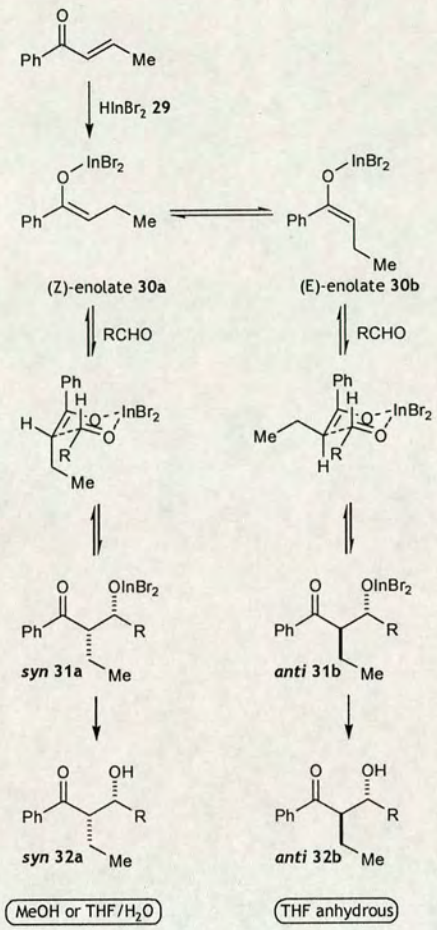
chlorides using a combination of indium(III) halides and *n*-Bu_3SnH,[31] Baba further extended this system to include the reductive aldol reaction between enones and substituted benzaldehydes (Table 1.22).



R	Solvent	%Yield	*syn:anti*
4-MeOPh	THF	86	4:96
4-MeOPh	MeOH	69	>99:1
4-MeOPh	THF	89	4:96
4-MeOPh	THF/H_2O (9/1)	77	95:5
4-ClPh	THF	83	7:97
4-ClPh	MeOH	68	90:10

Table 1.22

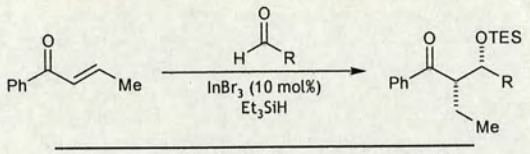
The reductive aldol adducts are obtained in moderate to good yield and with excellent diastereoselectivities of up to >99:1 (*syn*:*anti*) when MeOH or aqueous THF are used as solvents. Interestingly, the *anti* diastereomer can be readily obtained in excellent yields and with selectivities of up to 4:96 (*syn*:*anti*) when anhydrous THF is used as solvent. In addition, Baba further proposed a tentative mechanism for this diastereoselective reductive aldol methodology in an effort to account for the remarkable solvent effects (Scheme 1.14).



Scheme 1.14

The conjugate addition of indium hydride **29** occurs to generate initially the (Z)-enolate **30a** which reacts with the aldehyde *via* a Zimmerman-Traxler-type transition state[13] to give the *syn* aldol adduct **31a** which is rapidly protonated in MeOH or THF/H_2O. When anhydrous THF is used as solvent, retro aldol from the *syn* aldolate **31a** to the *anti* aldolate **31b** occurs under thermodynamic control which is then trapped by hydrolysis on reaction work-up.

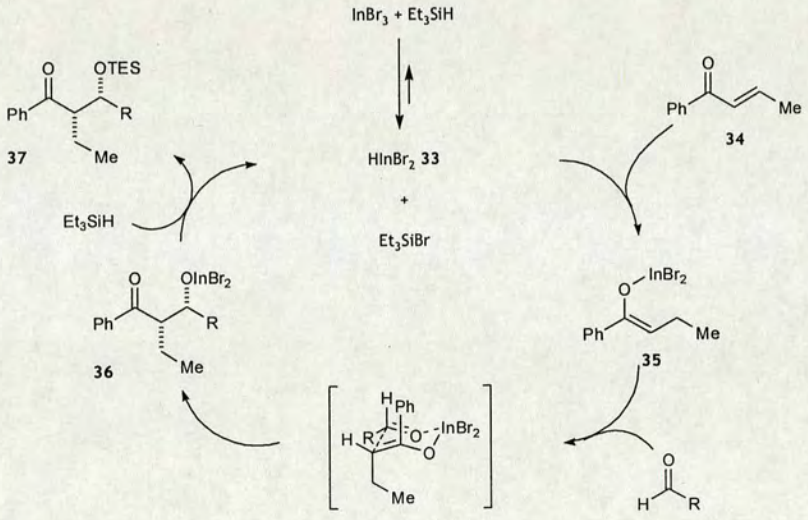
Despite the excellent results, this system requires stoichiometric quantities of indium salt and employs highly toxic tin hydride as the reductant. As a result, Baba has recently developed a catalytic approach using $InBr_3$ (10 mol%) and triethylsilane as the stoichiometric reductant (Table 1.23).[32]



R	%Yield	*syn:anti*
4-MeOPh	75	90:10
4-NO_2Ph	59	>99:1
Ph	78	92:8
Bn	40	>99:1
^{t}Bu	73	>99:1

Table 1.23

A variety of enone starting materials can be efficiently coupled with a range of aromatic and aliphatic aldehydes to give the corresponding aldol adducts in good yield and with diastereoselectivities of up to 99:1 (*syn:anti*). A plausible catalytic cycle was proposed which is similar to that previously discussed (Scheme 1.15).



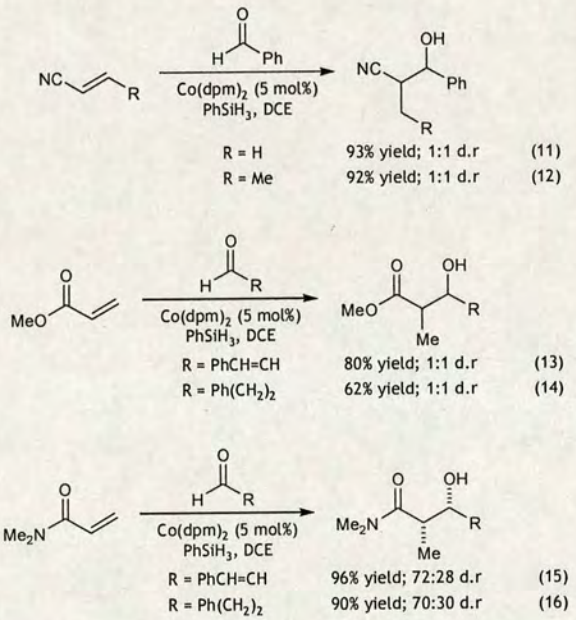
Scheme 1.15

The conjugate addition of indium hydride **33** into enone **34** occurs to generate the (*Z*)-enolate **35** which reacts with the aldehyde *via* a Zimmerman-Traxler-type transition state[13] to give the *syn* aldol adduct as the indium alkoxide **36**. Silylation

with another molecule of reductant gives the product as the silyl ether **37** and liberates the active catalyst to initiate another cycle.

1.7. Cobalt-catalysed intermolecular reductive aldol reactions

Following the pioneering work of Revis and Hilty,[2] Mukaiyama endeavored to uncover the potential of other transition metals to catalyse the reductive aldol coupling of various α,β-unsaturated nitriles (eq 11 and 12), esters (eq 13 and 14) and amides (eq 15 and 16) to aldehydes. Consequently, Mukaiyama and co-workers published the first example of a cobalt-catalysed intermolecular reductive aldol reaction.[33]

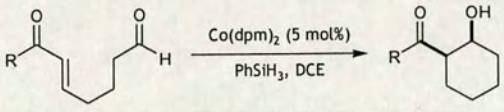


Mukaiyama demonstrated that α,β-unsaturated esters and nitriles couple efficiently to benzaldehyde and hydrocinnamaldehyde respectively in moderate to good yields but with no stereocontrol. On the other hand, α,β-unsaturated amides couple with a variety of aldehydes in excellent yields and with moderate levels of diastereoselection. Although no mechanistic rational was reported, Mukaiyama postulated that a carbon-bound cobalt enolate would result from the hydrometallation of the α,β-unsaturated component by a cobalt-hydride species. This would be

followed by reductive aldol coupling to the corresponding aldehyde aided by phenyl silane to liberate the β-siloxy aldol adducts which are hydrolysed during work-up to give the desired β-hydroxy carbonyl species.

1.8. *Cobalt-catalysed intramolecular reductive aldol reactions*

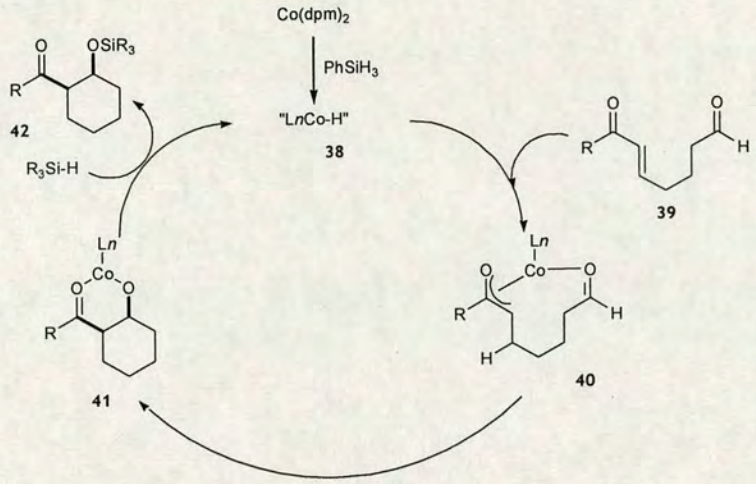
Using identical conditions to those discovered by Mukaiyama, Krische and co-workers were able to effect the highly diastereoselective reductive aldol cyclisation of a variety of α,β-unsaturated ketones tethered to an aldehyde through an all–carbon linkage (Table 1.24).[34]



R	%Yield	*syn:anti*
Ph	87	>99:1
4-CF_3Ph	72	>99:1
2-naphthyl	68	>99:1
Me	38	>99:1
2-furyl	75	>99:1
2-thiophene	73	>99:1

Table 1.24

Krische demonstrated that a variety of aromatic enones are tolerated under Mukaiyama's conditions[33] to produce the corresponding six-membered carbocycles in moderate to good yields and with exceptionally high levels of diastereoselection. In addition, Krische proposed a plausible mechanistic rational for the process (Scheme 1.16)

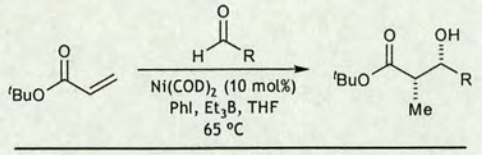


Scheme 1.16

The combination of $Co(dpm)_2$ and phenyl silane produces cobalt-hydride species **38** which, upon hydrometallation of the enone **39**, produces a chelated cobalt enolate **40**. Subsequent aldol cyclisation results in the formation of cobalt alkoxide **41**. σ-Bond metathesis of **41** with afu rther molecule of reductant liberates the silylated aldol product **42** and regenerates the cobalt-hydride catalyst **38**.[34, 35]

1.9. Nickel-catalysed intermolecular reductive aldol reactions

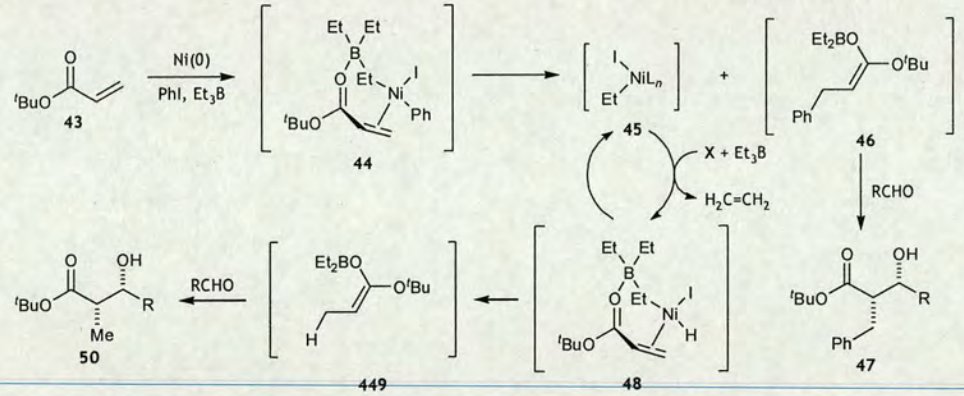
The first example of a nickel-catalysed reductive aldol process was reported by Montgomery and co-workers in 2007.[36] Montgomery elegantly demonstrated that substoichiometric quantities of $Ni(COD)_2$ in combination with stoichiometric amounts of triethylborane (Et_3B) and phenyl iodide (PhI) allowed *tert*-butyl acrylate to couple with a variety of aldehydes, producing the reductive aldol products in good yield and with good diastereoselectivities (Table 1.25).



R	%Yield	*syn:anti*
Ph	87	88:12
4-MeOPh	88	87:13
2-furyl	91	88:12
4-NCPh	86	90:10
$CH_3(CH_2)_5$	80	86:14
$(CH_3CH_2)_2CH$	68	96:4

Table 1.25

It was observed that the presence of PhI was essential for reaction efficacy and that in its absence the reaction failed to initiate. This type of effect has been noted in a related study by Cheng and co-workers describing the initiating effect of organic iodide species in palladium-catalysed silaboration of allenes.[37] In their work Cheng and co-workers suggested that the organic iodide species participates in the formation of a boron-containing side-product which then initiates the catalytic cycle. On the other hand, Montgomery and co-workers proposed that the presence of PhI in the reaction mixture results in a catalyst modification which then proceeds to initiate the reaction. As a result of experimental observation Montgomery proposed the following mechanism involving a novel catalyst activation sequence (Scheme 1.17).



Scheme 1.17

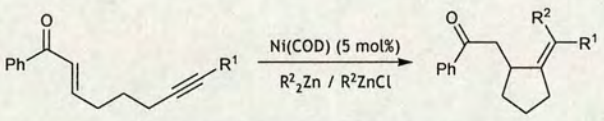
Initially, oxidative insertion of Ni(0) to phenyl iodide followed by coordination of acrylate **43** and triethylborane will give intermediate species **44**. Rearrangement of **44** to an ethyl(iodo)nickel species **45** and boron enolate **46** may well proceed through sequential migratory insertion and transmetalation. Triethylborane acts both as a Lewis acid and a Lewis base by activating the enone and nickel centre simultaneously.[38] The aldol addition of boron enolate **46** with the aldehyde generates product **47**. The ethyl(iodo)nickel species **45** complexes with the acrylate **43** and a further molecule of triethylborane with the subsequent loss of ethylene to generate nickel hydride **48**. Rearrangemnet of **48** results in the formation of boron enolate **49** and regenerated ethyl(iodo)nickel species **45**. The aldol addition of **49** with the aldehyde affords product **50**, the major product of the reaction.

2. Nickel-Mediated Reductive Coupling Reactions

Nickel-catalysed reductive coupling and cyclisation reactions have emerged as important methodologies in the construction of various polyfunctionalised compounds. The reductive coupling of unsaturated species such as: alkynes, 1,3-dienes, 1,3-enynes and allenes with a variety of electrophiles including aldehydes, ketones, imines and epoxides can be accomplished under mild conditions using substoichiometric quantities of an appropriate nickel salt and stoichiometric quantities of a reductants such as, diethylzinc, triethylborane or silanes. Through the use of chiral non-racemic ligands as additives in the reductive coupling reactions the products can often be generated with high levels of diastereo- and enantiocontrol.

2.1. Intramolecular nickel-mediated reductive coupling reactions

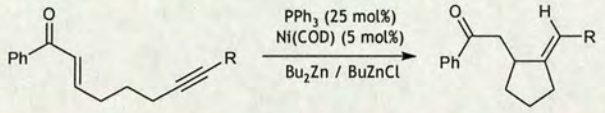
Nickel-catalysed reductive cyclisation reactions were pioneered by Montgomery and co-workers in 1996.[39] Following the observation by MacKenzie and co-workers that nickel(0)-species undergo oxidative addition reactions to enals in the presence of a Lewis-acid additive,[40] Montgomery demonstrated that this fundamental process could be efficiently utilized in the nickel-catalysed alkylative cyclisation of alkynyl enones (Table 2.1).[39]



R^1	R^2	%Yield
H	Me	82
H	Bu	51
H	Ph	61
H	$CH=CH_2$	59
Ph	Bu	68
Bu	Ph	38

Table 2.1

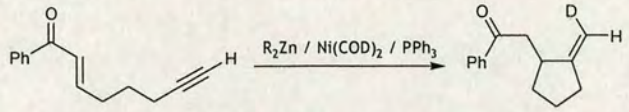
A variety of alkyl-, alkenyl- and aryl-substituted organozinc reagents, including those bearing β-hydrogens, were shown to promote efficient cyclisations, producing the corresponding β-alkenyl ketones in moderate to good yield and with complete control of olefin geometry. In addition to alkylative cyclisations, Montgomery and co-workers demonstrated that reductive cyclisations could be obtained through the pre-treatment of $Ni(COD)_2$ with 5 equivalents of triphenylphosphine in combination with dibutylzinc as the reductant (Table 2.2).



R	%Yield
H	92
Ph	47
Bu	58

Table 2.2

Similar to the results detailed in (Table 2.1), the cyclisations occur in moderate to good yield with complete control of the olefin geometry, delivering the hydride *cis* to the ketone in all cases. Notably, when alternative organozinc reagents were used such as, dimethylzinc or diphenylzinc, only alkylative cyclisation is observed even in the presence of 5 equivalents of triphenylphosphine. As a consequence, Montgomery proposed that when using dibutylzinc as the reductant the reaction can proceed through a competitive β-hydride elimination pathway promoted by the presence of triphenylphosphine. In an effort to confirm the involvement of a β-hydride elimination pathway in the reductive cyclisation reactions, several deuterium labelling experiments were conducted (eq 17-19).

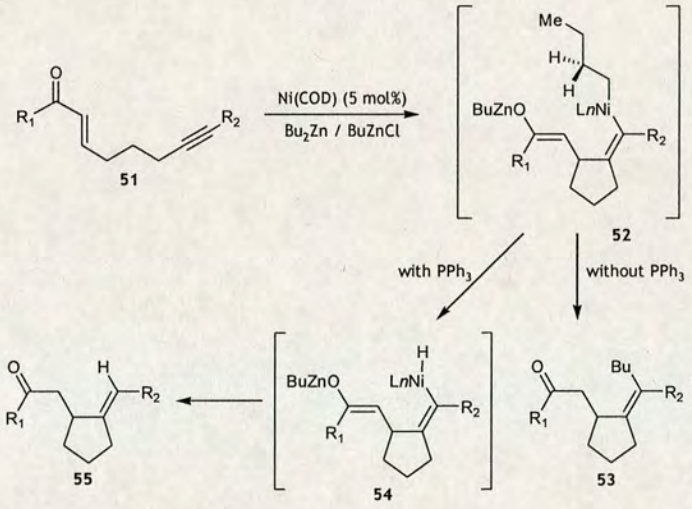


with Et_2Zn-d_{10} in THF, then H_2O quench: **68%** D incorporation (17)

with Bu_2Zn in THF, then AcOD quench: **12%** D incorporation (18)

with Et_2Zn in THF-d_8, then H_2O quench: **0%** D incorporation (19)

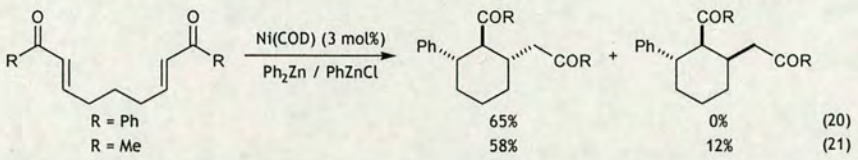
From these results it was reasoned that two reaction pathways are operative. The major pathway involves β-hydride elimination whereas the minor pathway involves the protonation of a zinc-alkenyl-species on work-up. As a result of these findings Montgomery speculated that the reaction proceeds through the following pathway (Scheme 2.1).



Scheme 2.1

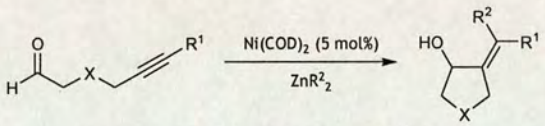
It was suggested that in the absence of triphenylphosphine intermediate **52** could coordinate with unreacted enone starting material **51** and through the formation of an electron-deficient Ni(II) π-complex,[41] promote the reductive elimination affording the alkylative cyclisation products **53** (Table 2.1). However, in the presence of triphenylphosphine the alkyl(alkenyl)nickel intermediate **54** would be more electron-rich at nickel and therefore, facilitating β-hydride elimination to produce the reductive cyclisation products **55** (Table 2.2).[42]

Montgomery and co-workers further extended their methodology to include the cyclisation of bis-enones (eq 20 and 21).[43]



In this example, the cyclisation reaction proceeds through a mechanism involving sequential conjugate addition reactions. This reaction pathway is in stark contrast to that of the cyclisation of alkynyl-enone substrates where conjugate addition was not observed.[39]

In addition, it was demonstrated by Montgomery and co-workers that allylic alcohols could be efficiently synthesised through the application of their nickel-catalysed alkylative coupling methodology to the cyclisation of ynals (Table 2.3).[44]

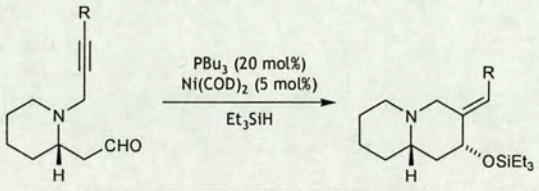


X	R^1	R^2	%Yield
CH_2	H	CH_3	70
CH_2	H	Ph	72
CH_2	H	*n*-Bu	62
CH_2	CH_3	Ph	64
CH_2	CH_3	*n*-Bu	76
CH_2	Ph	CH_3	73
CH_2	Ph	Et	67
NCOPh	H	CH_3	72

Table 2.3

The combination of substoichiometric quantities of $Ni(COD)_2$ and stoichiometric quantities of a variety of dialkylzinc reagents results in the alkylative cyclisation of an array of ynals giving the products in moderate yields and with complete control of the olefin geometry. Alternatively, by the replacement of dialkylzinc reagents with

silane reductants and by the addition of a phosphine additive, Montgomery illustrated that protected allylic alcohols could be readily synthesised through the application of their nickel-catalysed reductive coupling methodology (Table 2.4).[45]

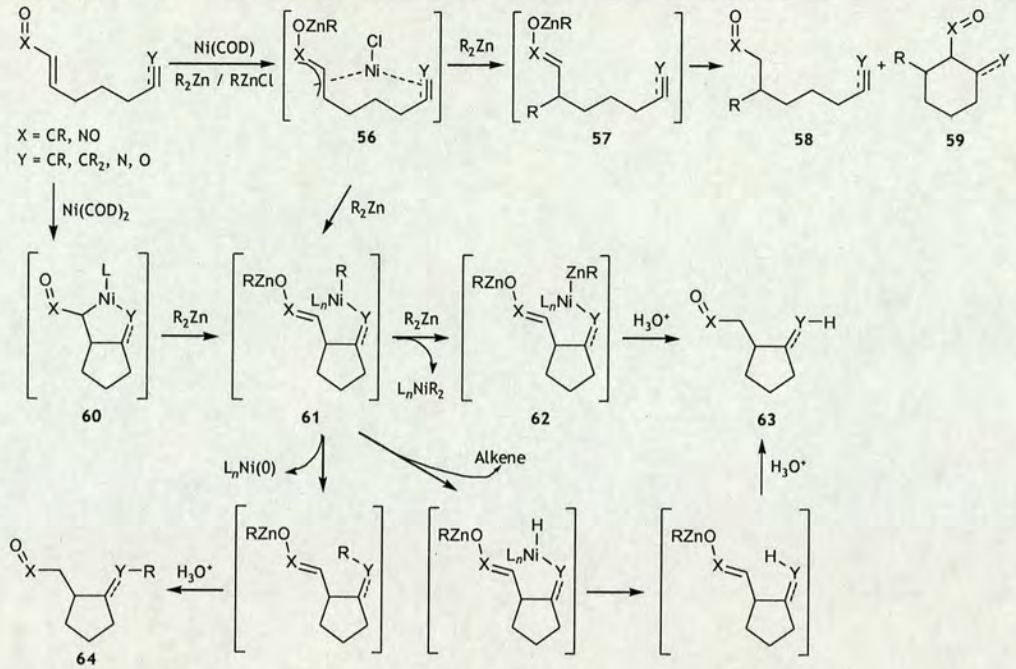


R	T(°C)	dr	%Yield
Ph	45	90:10	85
Ph	23	98:2	90
Ph	0	>97:3	89
$SiMe_3$	45	98:2	93
n-C_6H_{13}	45	99:1	83
H	45	95:5	81

Table 2.4

As previously illustrated (Scheme 2.1), the addition of phosphine additives results in the formation of the reductively coupled products. In this case a variey of ynals cyclised efficiently giving the silylated allylic alcohols in excellent yield and with excellent levels of diastereoselectivity.

Through their extensive research in the area Montgomery and co-workers proposed a detailed mechanism for both the reductive and alkylative cyclisation reactions (Scheme 2.2).[46]

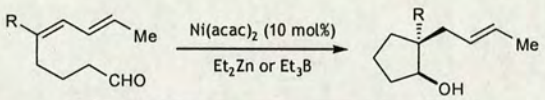


Scheme 2.2

They speculate that two general mechanistic pathways lead to common intermediate **61**. The first pathway is analogous to the studies carried out by MacKenzie[40] which involves the oxidative addition of a low valent nickel catalyst to an organozinc-activated electron-deficient alkene to produce nickel π-allyl complex **56**. If the organozinc species rapidly transmetalates to nickel or if the coordinated olefin is sufficiently deactivated then π-allyl complex **56** may undergo a transmetalation/reductive elimination sequence to produce enolate **57**, resulting in conjugate addition products **58** or **59**. Alternatively, cyclisation of species **56** would afford intermediate **61**. The second pathway is analogous to the mechanism of zirococene-catalysed cyclomagnesiations of dienes,[47] involving the oxidative cyclisation to produce metallacycle **60**. However, additional mechanistic studies carried out by Montgomery and co-workers indicate that metallacycle **60** forms *via* a [3 + 2] cycloaddition with Ni(0).[48] Subsequent transmetalation of metallacycle **60** with a further molecule of organozinc reagent would afford intermediate **61**. With substrates containing tethered enone or aldehyde moieties, intermediate **61** would be

liable to undergo ligand displacement by reaction with the organozinc reagent to generate intermediate **62** which is then hydrolysed to reductive cyclisation product **63** on work-up. With substrates tethered to alkynes, intermediate **61** undergoes a reductive elimination in the absence of a phosphine ligand to produce the alkylative cyclisation product **64**. In the presence of a phosphine ligand, β-hydride elimination occurs instead to produce the reductive cyclisation product **63**.

Since then, Tamaru and co-workers have extended the scope of nickel-catalysed reductive cyclisation reactions to encompass intramolecular homoallylation of a variety of ω-dienyl aldehydes.[49] Through a combination of $Ni(acac)_2$ and either diethylzinc or triethylborane as the stoichiometric reductant, an array of substrates cyclised in moderate to good yield (Table 2.5).

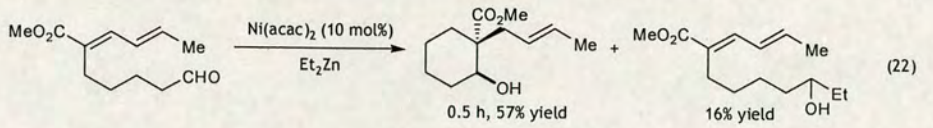


R	Reductant	Time (h)	%Yield
CO_2Me	Et_2Zn	0.25	72
CO_2Me	Et_3B	34	67
CH_2OBn	Et_2Zn	0.25	64[a]
CH_2OBn	Et_3B	24	80
CH_2OBz	Et_2Zn	0.5	66
CH_2OBz	Et_3B	24	27

[a]Competitive ethyl addition into aldehyde

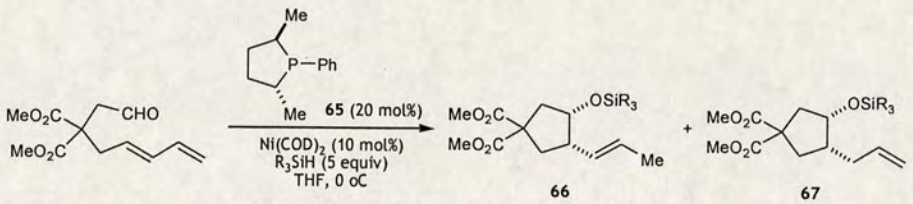
Table 2.5

It was observed that diethylzinc was the most effective reductant in terms of the reaction rate compared to triethylborane. However, in some cases the use of diethylzinc resulted in the competitive ethyl addition to the pendant aldehyde producing the corresponding secondary alcohol, for example (eq 22).



(22)

Another research group working extensively in the area of nickel-catalysed reductive cyclisation reactions is that of Miwako Mori. Mori and co-workers have published many articles concerning developments of stereoselective nickel-catalysed cyclisations of 1,3-dienes with tethered carbonyl groups for the synthesis of five- to seven-membered carbocycles,[50] heterocycles[51] and bicyclic heterocycles.[51,52] In 2002 Mori and co-workers reported the development of an asymmetric cyclisation of ω-formyl-1,3-dienes mediated by substoichiometric quantities of $Ni(COD)_2$ and a chiral non-racemic mono-dentate phosphine ligand **65** in the presence of silanes as the reductant (Table 2.6).[53]



R_3SiH	%Yield	66:67	ee% 66(67)
Et_3SiH	84	4.3:1	2(47)
$^tBuMe_2SiH$	83	>50:1	16(-)
$(EtO)_3SiH$	60	12:1	46(33)
Ph_3SiH	80	1.7:1	47(53)
Ph_2MeSiH	83	1.2:1	27(78)
$PhMe_2SiH$	82	1.9:1	21(72)
Ph_2MeSiH	73	1:1.2	44(86)[a]

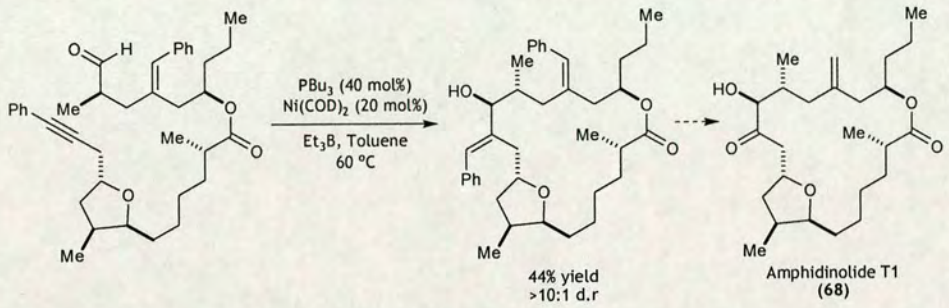
[a]DMF / -20 °C

Table 2.6

The reaction is effectively mediated by a large variety of silanes, giving the products in up to 84% yield. However, double bond isomerisation presents a problem with geometric isomers **66** and **67** being produced in almost equal amounts when aryl

silanes ared used as the reductant. Nevertheless, the use of Ph_2MeSiH allows the synthesis of **67** to be accomplished in an excellent 86% enantiomeric excess.

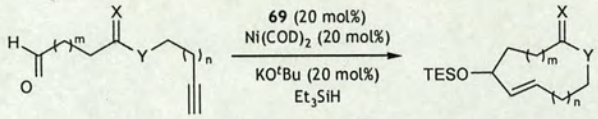
More recently Jamison and co-workers have demonstrated the broad synthetic utility of stereoselective nickel-catalysed reductive cyclisation methodology by applying it to the synthesis of the18-membered macrocycle in the natural product amphidinolide T1 **(68)** (eq 23).[54]



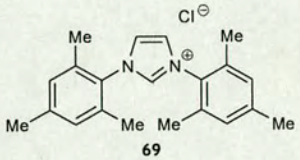
(23)

Using substoichiometric quantities of $Ni(COD)_2$ and tributylphosphine in the presence of triethylborane as the reductant enabled the construction of the 18-membered ring in an impressive 44% yield and with good diastereoselectivity (>10:1).

In addition, Montgomery and co-workers have reported that by using *N*-heterocyclic carbene ligands in place of mono-dentate phosphines such as tributylphosphine; macrocycles of up to 22-membered rings can be constructed using nickel-catalysis (Table 2.7).[55]



X	Y	*m*	*n*	Ring Size	%Yield
H_2	CH_2	1	3	11	50
H_2	CH_2	1	6	14	62
O	O	7	3	15	69
O	O	7	5	19	70
O	O	7	8	22	67



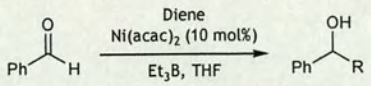
69

Table 2.7

It was demonstrated that large macrocyclic ring systems could be synthesised in moderate yield with only the endocyclic product being observed.

2.2. *Intermolecular nickel-mediated reductive coupling reactions*

Tamaru and co-workers demonstrated in 1998 that the combination of substoichiometric quantities of $Ni(acac)_2$ and triethylborane as the reductant, efficiently mediates the homoallylation of benzaldehyde in high yields and selectivities (Table 2.8).[56]



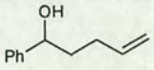
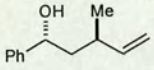
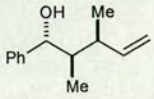
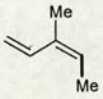
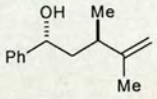
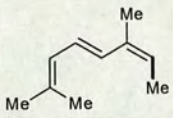
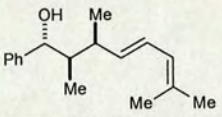
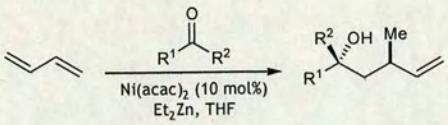
Diene	Time (h)	Products	*syn:anti*	%Yield
	21		na	77
	35		1:15	90
	41		N.D	86
	23		8:1	94
	28		15:1	95

Table 2.8

The reaction tolerates a wide variety of diene coupling partners, generating the products in up to 95% and with excellent levels of 1,2-stereoselection. Furthermore, reduced amounts of nickel catalyst can be readily tolerated, with 1 mol% of $Ni(acac)_2$ resulting in similar levels of conversion and selectivity in the majority of cases. Subsequent to these results, Tamaru and co-workers reported the extension of their nickel-catalysed homoallylation methodology of benzaldehyde[56] to include a number of diverse aldehydes and ketones, utilising diethylzinc as the stoichiometric reductant (Table 2.9).[57, 58]



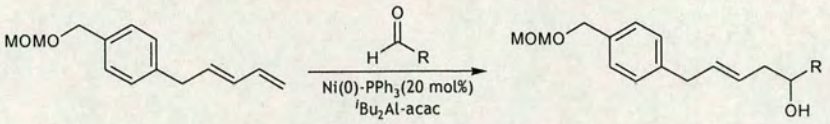
R^1	R^2	*syn:anti*	%Yield
Ph	H	1:15	63
2-furyl	H	1:3	66
PhCH=CH	H	-	0
$PhCH_2CH_2$	H	1:15	73
^{t}Bu	H	1:15	66
Me	Me	5.3:1	69[a]

[a]Regioisomeric mixture (4-Me) and (5-Me)

Table 2.9

A variety of aldehydes were shown to be competent coupling partners giving the corresponding homoallyl products in moderate yield and with excellent levels of 1,3-*anti*-selectivity in the majority of cases. On the other hand, the use of acetone as the coupling partner gave the corresponding product as a mixture of regioisomers. Notably, the use of diethylzinc in place of triethylborane led to increased reaction rates with complete conversion of starting materials after 1 hour in most cases.

Using a combination of Ni(0)-PPh_3 (synthesised from a BuLi addition into a solution of $NiCl_2(PPh_3)_2$) and $^t Bu_2$Al-acac Mori and co-workers were able to couple a range of aryl and aliphatic aldehydes to a substituted 1,3-diene (Table 2.10).[59]



R	%Yield
Ph	62
4-MeOPh	78
MeO_2C	34
$c\text{-}C_6H_{11}$	62
^{i}Pr	57
^{n}Pr	26

Table 2.10

The coupling reaction gave the products in moderate yields and with complete control of the olefin geometry (*E*-isomer). However, the yields were reduced somewhat by the competitive formation of the regioisomeric branched adduct shown (Figure 2.1).

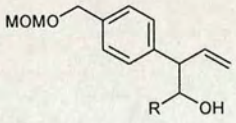
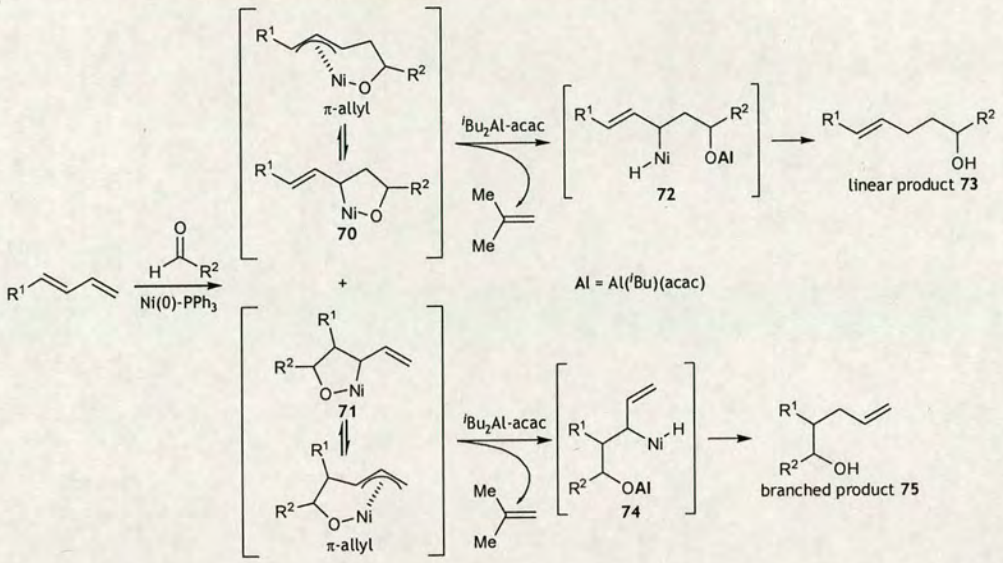


Figure 2.1

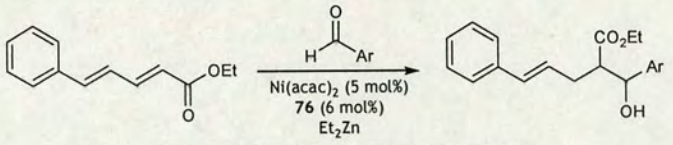
Moreover, Mori proposed the following outline mechanism to account for the experimental observations (Scheme 2.3).



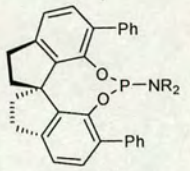
Scheme 2.3

Linear adduct **73** would be produced *via* nickelacycle **70**. Transmetallation of nickelacycle **70** with $^{i}Bu_2Al$-acac followed by β-hydride elimination with concominant evolution of isobutene, would give nickel-hydride species **72**. Reductive elimination followed by reaction work-up would give linear product **73**. The branched adduct **75** would be formed *via* nickelacycle **71** in a similar fashion to that described for the linear product **73**.

Further developments in the area of nickel-catalysed additions of dienes to aldehydes have emerged from the laboratory of Zhou and co-workers. In 2007 they described the homoallylic coupling of a substituted diene to a variety of aromatic aldehydes, generating the corresponding products in excellent yields and with remarkable levels of both diastereo- and enantioselectivity (Table 2.11).[60]



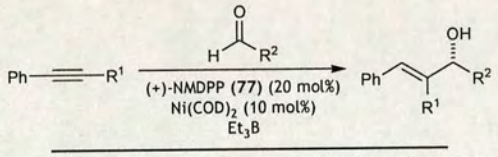
Ar	*syn:anti*	%Yield	%ee
Ph	>1:99	99	96
2-MeOPh	>1:99	98	91
4-MeOPh	>1:99	94	96
4-ClPh	>1:99	92	90
2-naphthyl	>1:99	96	86
2-furyl	>1:99	96	92



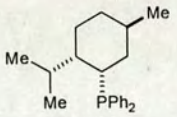
R = Morpholine
76

Table 2.11

More recently, Jamison andco -workers described the first example of a highly enantioselective method for the nickel-catalysed reductive coupling of alkynes to aldehydes (Table 2.12).[61]



R^1	R^2	%Yield	%ee
Me	^{i}Pr	95	90
Me	c-C_6H_{11}	97	90
Me	^{n}Pr	82	65
$SiMe_3$	^{n}Pr	43	92
CH_2NHBoc	^{i}Pr	60	96
^{n}Pr	^{i}Pr	35	42

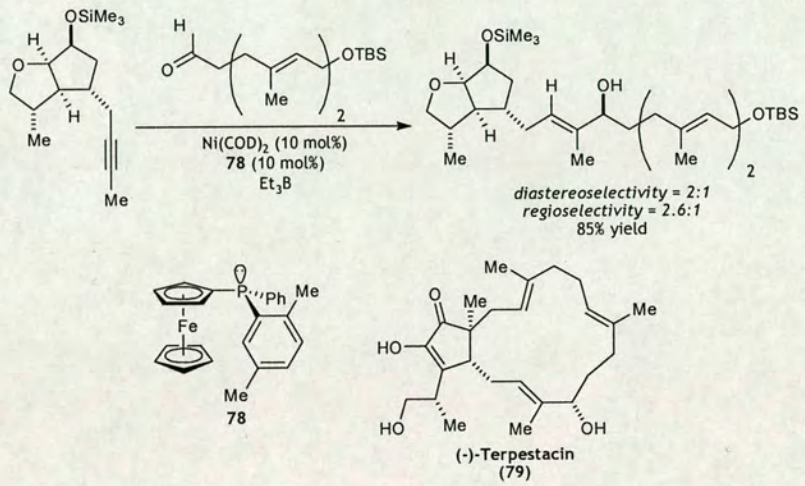


(+)-NMDPP
(77)

Table 2.12

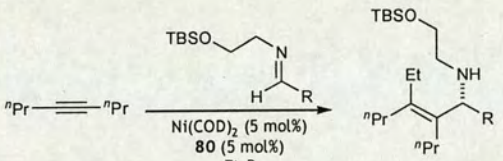
Using a combination of $Ni(COD)_2$ and the mono-dentate phosphine ligand (+)-NMDPP **(77)** in the presence of triethylborane a variety of substituted alkynes gave the corresponding allylic alcohol products in moderate to excellent yields and with generally excellent levels of enantioselectivity. Most notably, in all cases examined only the *cis*-olefin geometry was obtained. Moreover, Jamison and co-workers

utilized this methodology to great effect in the key-step in the synthesis of the natural product (-)-Terpestacin **(79)** (eq 24).[62]



(24)

In addition, Jamison and co-workers extended their methodology to include the enantioselective nickel-catalysed alkylative coupling of an aliphatic alkyne to a variety of aryl imines (Table 2.13).[63,64]



R	%Yield	%ee
Ph	85	89
2-MePh	74	85
4-MeOPh	75	82
4-CF_3Ph	91	85
2-napthyl	90	73

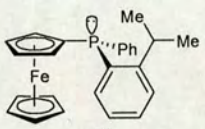
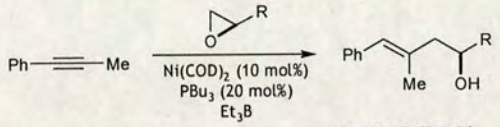


Table 2.13

By using triethylborane in combination with substoichiometric quantities of $Ni(COD)_2$ and a P-chiral ferrocenyl phosphine ligand **80**, this three-component

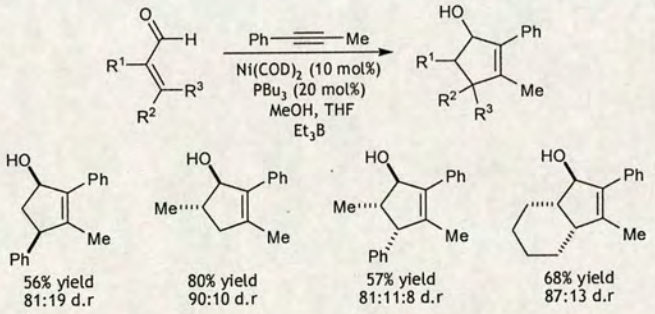
coupling reaction smoothly provided the allylic amine products in moderate to excellent yield and with good enantioselectivity.

Moreover, Jamison and co-workers demonstrated that other electrophilic species could be effective coupling partners in their nickel-catalysed reductive coupling methodology. For example, a variety aliphatic epoxides were shown to couple with an aryl alkyne in moderate yield and with complete control of olefin geometry (eq 25-27).[65]



R = Me; 71% yield (25)
R = *n*-Hex; 68% yield (26)
R = Ph; 50% yield (27)

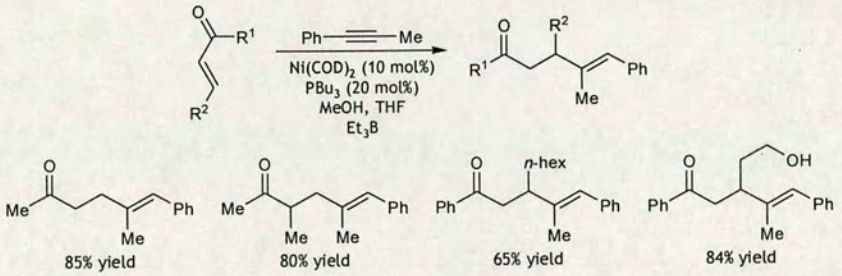
The contruction of five-membered rings is an important goal in synthetic chemistry. In this regard, Montgomery and co-workers recently reported a nickel-catalysed [3 + 2] reductive cycloaddition methodology of enal-alkyne systems that readily provided cyclopentanols in moderate yields and with good diastereoselectivities (Scheme 2.4).[66]



Scheme 2.4

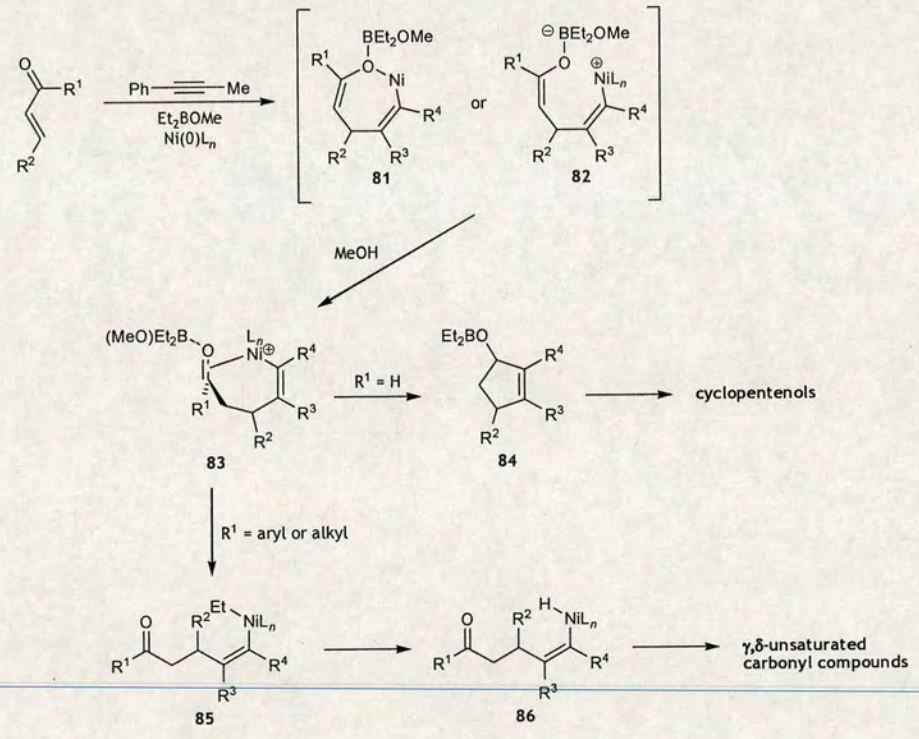
Conversely, by using enone compounds as coupling partners instead of enals, the reaction proceded through an intermolecular reductive coupling pathway producing

the corresponding γ,δ-unsaturated carbonyl compounds in good yield and with excellent diastereoselectivities (>95:5) (Scheme 2.5).[67]



Scheme 2.5

Montgomery describes the divergent reactivity of enones compared with enals within the same mechanistic pathway as catalytic [3 + 2] reductive cycloadditions (Scheme 2.6).



Scheme 2.6

Initial oxidative cyclisation of the enone and alkyne with Ni(0) would produce metallacycle **81** or alternatively the borane adduct **82**.[68,69] Protonation of intermediate **81** or **82** would afford intermediate **83**. From this intermediate if using an enal (R^1 = H), vinyl nickel addition to the tethered aldehyde would occur giving boron alkoxide **84**, which following reaction work-up produces the cyclopentenol products as described (Scheme 2.4). On the other hand, if using an enone (R^1 = aryl or alkyl) then carbonyl addition is sterically impeded resulting in the ethyl transfer from boron to nickel producing **85**. This is followed by β-hydride elimination to **86** and subsequent reductive elimination generates the reductive coupling products as described (Scheme 2.5).

3. Copper-Catalysed Reductive Aldol Cyclisations

The abundance of heterocyclic structures in many biologically significant natural products and pharmaceutical agents, such as salinosporamide A **(87)**[70] and morphine **(88)**, makes the pursuit of an efficient and stereoselective synthesis of heterocyclic targets an immensely important goal in synthetic chemistry (Figure 3.1).

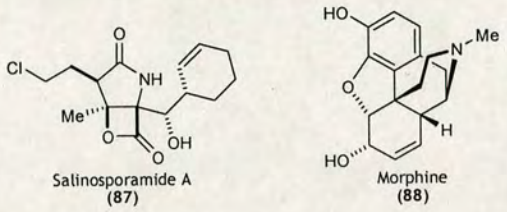
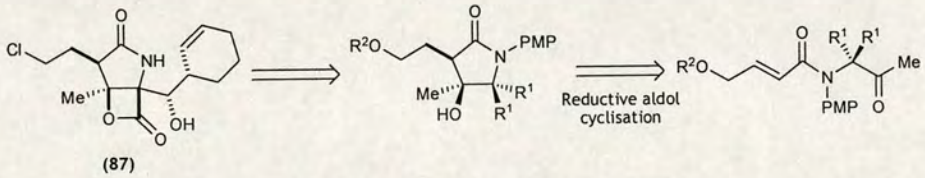


Figure 3.1

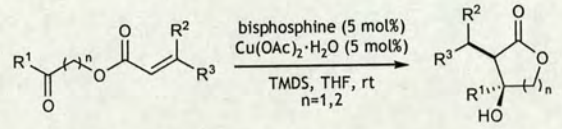
In this regard the Lam group has previously demonstrated the application of reductive aldol chemistry in the enantioselective synthesis of a number of five- and six- membered β-hydroxylactones (Scheme 1.13).[27] Through the extension of this methodology we surmised that a variety of α,β-unsaturated carbonyl compounds tethered to ketones through an amide linkage would lead to the stereoselective synthesis of five- and six-membered β-hydroxylactams. If successful, this methodology could form the basis of a novel and highly efficient total synthesis of salinosporamide A **(87)**[71] (Scheme 3.1).



Scheme 3.1

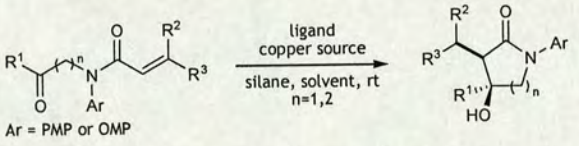
3.1. Results and Discussion[72]

As previously described (Chapter 1.4) initial work within the Lam group had identified an effective catalyst system for the reductive aldol cyclisation of α,β-unsaturated carbonyl compounds tethered to ketones through ester linkages (eq 28).[27] The catalyst system based on Buchwald's[19a] methodology for the conjugate reduction of enones offered an excellent foundation for further exploration of reaction conditions.



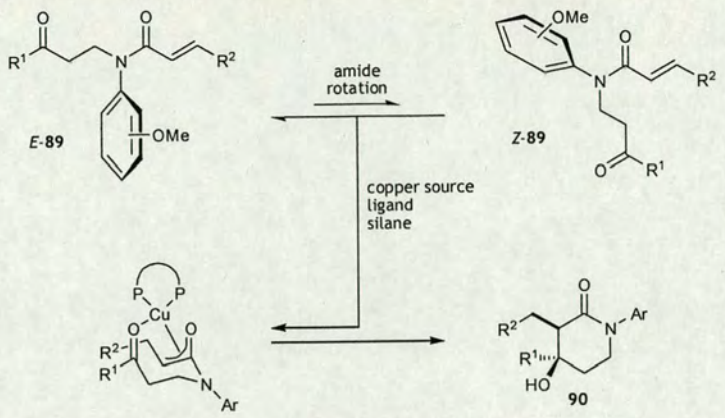
(28)

For our initial studies, we looked at the synthesis of 4-hydroxypiperidin-2-ones with variations in the choice of copper(II) salt, silane reductant and solvent (eq 29). In order to increase the synthetic versatility of the products we opted to examine substrates containing removable nitrogen protecting groups such as PMP (*p*-methoxyphenyl)[73] and OMP[73, 74] (*o*-methoxyphenyl).



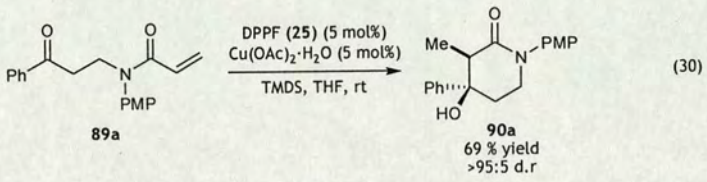
(29)

At the commencement of this program of research we were aware that *N*-alkyl-*N*-arylamides such as **89** are known to exist predominately as the *E*-amide rotamer (Scheme 3.2).[75] As a consequence it was unknown as to whether this rotamer distribution would have any impact on the reactivity of these substrates.



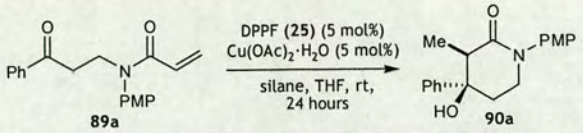
Scheme 3.2

Nevertheless, using the conditions previously developed within the group,[27] substrate **89a** underwent cyclisation to form 4-hydroxypiperdin-2-one **90a** in 69% yield and with a diastereoselectivity of >95:5 (eq 30).



(30)

Alternative copper(II) salts[76] were examined for efficacy; however, none proved to be as effective as $Cu(OAc)_2 \cdot H_2O$ in terms of reactivity. Furthermore, silane structure has been noted to have significant effects on both the reactivity and selectivity of reductive aldol reactions.[5] To this end, we explored a number of structurally diverse silanes (Table 3.1).

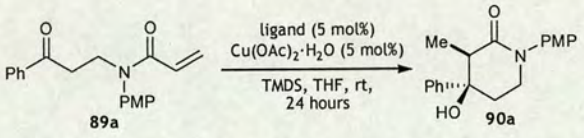


Silane	Equivalents	%Conversion[a]
TMDS	1.2	>95
$(EtO)_2MeSiH$	1.2	>95
$(EtO)_3SiH$	1.2	>95
PMHS	4.0	~70
$PhSiH_3$	2.0	<5
$PhMe_2SiH$	2.0	<5
Et_3SiH	2.0	<5

[a]Determined by ^1H NMR analysis of the unpurified reaction mixtures

Table 3.1

It was observed that alkoxy silanes ($(EtO)_2MeSiH$ and $(EtO)_3SiH$) and siloxanes (TMDS and PMHS) were efficient reductants. However, alkyl (Et_3SiH) and aromatic ($PhMe_2SiH$ and $PhSiH_3$) silanes proved to be ineffective. The use of TMDS as the reductant was considered to be more favourable in terms of its availability and cost. In addition, it has been noted in a variety of reported reductive aldol reactions that the structure of the complexing ligand plays a pivotal role in the efficiency of the reaction. Therefore, to explore these effects in our system we investigated a number of bidentate phosphine ligands (Table 3.2).



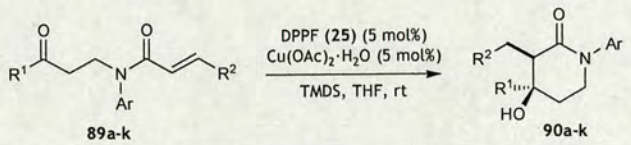
Ligand	%Conversion[a]
DPPF (25)	>95
rac-BINAP	>95
DPPE	<5
DPPB	<5

[a]Determined by ^1H NMR analysis of the unpurified reaction mixtures

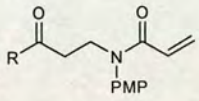
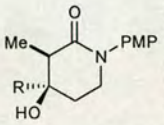
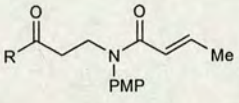
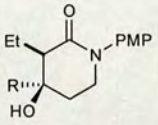
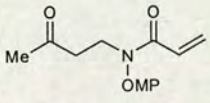
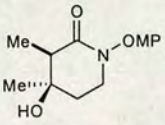
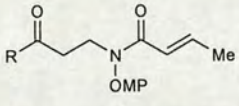
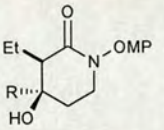
Table 3.2

Of the ligands tested *rac*-BINAP and DPPF **(25)** performed with similar efficacy, with poor conversion being observed for DPPE and DPPB. As a result, DPPF **(25)** was chosen for subsequent experiments based on its availability and cost. Moreover,

reactions in alternative solvents such as toluene, dichloromethane or acetonitrile were observed to be sluggish. Therefore, with optimised conditions in hand a range of substrates **89a-k** underwent cyclisation to form 4-hydroxypiperidin-2-ones **90a-k** (Table 3.3).



89a-k **90a-k**

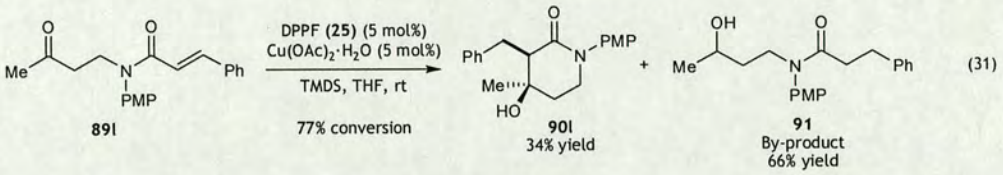
Entry	Substrate		Product		Time(h)	%Yield
1		R = Ph **89a**		**90a**	21	69
2		R = Et **89b**		**90b**	5.5	61
3		R = ^{t}Bu **89c**		**90c**	24	64
4		R = Me **89d**		**90d**	2.5	66
5		R = 4-MePh **89e**		**90e**	24	64
6		R = 2-furyl **89f**		**90f**	24	53
7		R = Me **89g**		**90g**	22	55
8		R = Et **89h**		**90h**	24	52
9		**89i**		**90i**	4	70
10		R = Me **89j**		**90j**	24	70
11		R = Ph **89k**		**90k**	23	65[a]

[a] $(EtO)_2MeSiH$ (2.0 mmol) was employed in place of TMDS

Table 3.3

The reaction tolerated wide variations in the ketone component with alkyl (entries 2-4 and 7-10), aromatic (entries 1, 5 and 11) and heteroaromatic (entry 6) ketones reacting readily. However, the reaction was far less tolerant of substitution in the α,β-unsaturated carbonyl component. Acryloyl amides proved to be the most reactive substrates, giving the reductive aldol products in all cases examined. Even though crontonyl amides underwent cyclisation, reaction rates and conversions were lower, in the majority of cases. In general, as the steric bulk of the substituent on the α,β-unsaturated carbonyl component increases, the formation of uncyclised side

products resulting from both ketone reduction and conjugate reduction becomes problematic (eq 31).

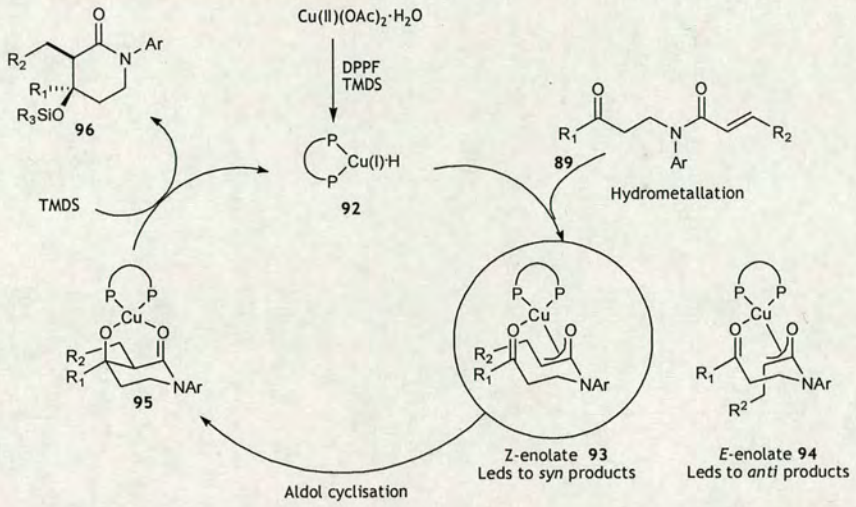


(31)

For example, the reductive aldol cyclisation of cinnamic derivative **89l** was observed to be very inefficient, giving only 77% conversion after 24 hrs. Analysis of the product distribution by proton NMR spectroscopy indicated that the major product formed was the uncyclised, doubly reduced starting material **91**. In cases where reaction turnover was observed to be problematic, alternative silanes could be used to good effect. For example, the reductive aldol cyclisation of substrate **89k** in the presence of TMDS proved sluggish. Nevertheless by changing the silane for $(EtO)_2MeSiH$ allowed the product to form in 65% yield over 23 hrs. Proton NMR spectroscopy of the crude product material indicates that all reactions proceed with high levels of diastereoselection (>95:5).

3.1.1. Proposed Mechanism

The proposed mechanism for this transformation bears similarities to the previously reported mechanistic details for the rhodium-catalysed reductive aldol reaction (Scheme 3.3).[8]



Scheme 3.3

Treatment of $Cu(OAc)_2 \cdot H_2O$ with TMDS in the presence of DPPF results in the formation of a copper(I) hydride species **92**. Hydrometallation of substrate **89** with **92** generates a chelated copper enolate **93**. The enolate generation is most likely to be highly *Z*-selective, owing to the exclusive formation of the *syn* aldol products. Enolate **93** then undergoes aldol cyclisation to give the copper alkoxide **95** which is followed by a σ-bond metathesis with another molecule of reductant to liberate the silated product **96** and regenerate the copper hydride catalyst **92**.

The relative configurations of products (**90a**, **90d** and **90g**) were confirmed by X-ray crystallography and reflected those of the lactone products previously reported from the Lam group (Figure 3.2).[27]

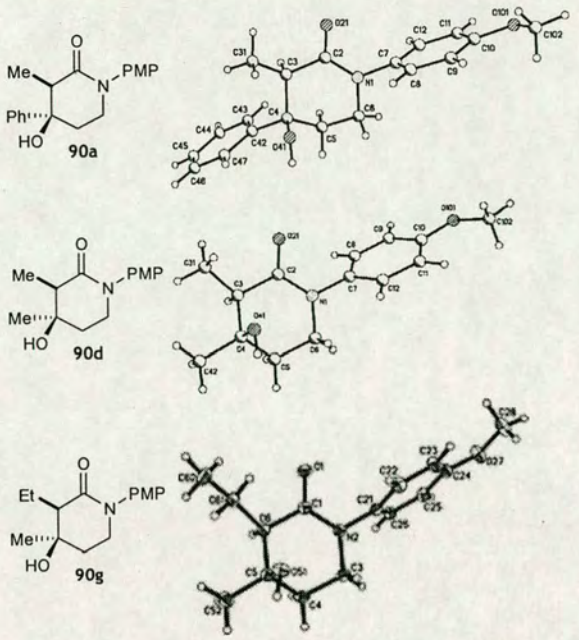
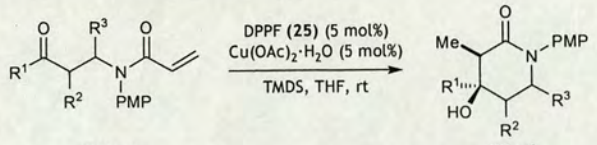
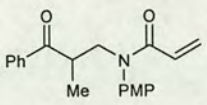
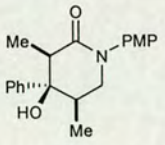
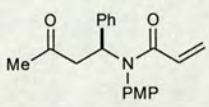
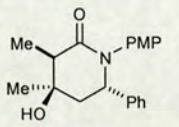
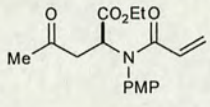
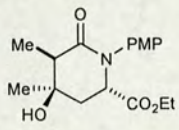
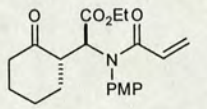
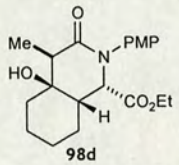


Figure 3.2

We postulated that the high levels of diastereoselectivity observed were due to both selective *Z*-enolate formation and chelation control in the six-membered Zimmerman-Traxler-like transition state.[13] To investigate the effect of pre-existing stereocentres on the diastereoselectivity of the process, a number of complex substrate molecules were synthesised (**97a-d**). Substrates **97b-d** were constructed in enantiomerically enriched form *via* an L-proline-catalysed asymmetric Mannich reaction as detailed in the experimental (Section 3.3). In addition, acrylamide substituted substrates were chosen due to their previously observed greater reactivity under our standard reaction conditions (Table 3.4).



97a-d 98a-d

Entry	Substrate	Product	d.r[a]	%Yield
1	 97a	 98a	8:1	78
2	 97b 85% ee	 98b	>19:1	65
3	 97c 96% ee	 98c	>16:1	68
4	 97d >99% ee	 98d	5:1	66

[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures

Table 3.4

Substrate **97a** (entry 1) containing an α-methyl substituent cyclised to give an 8:1 mixture of diastereomers, from which the major product **98a** was isolated in 78% yield. Cyclisation of substrates **97b-d** (entries 2-4) gave piperidinones **98b-d** in good yield and with moderate to good diastereoselectivities. Moreover, the observed levels of 1,2- and 1,3-asymmetric induction in these cyclisations may be rationalised by considering the chelated chairlike transition states (Figure 3.3) with substituents preferring to adopt a pseudoequatorial conformation. The relatively poor levels of diastereoselection obtained for **98d** is most likely due to the α-substituent being forced into an energetically unfavourable pseudoaxial position in the transition state **D**.

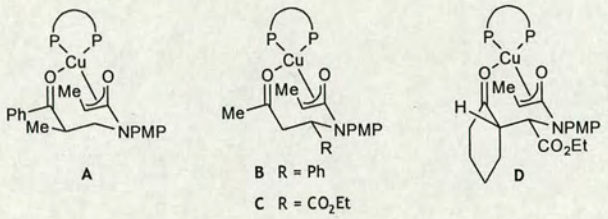


Figure 3.3

The benzylic proton in piperidinone **98b** was found to reside in a pseudoaxial position on the basis of the large axial-axial coupling constant of 11.3 Hz. Therefore, the phenyl substituent occupies a pseudoequatorial position. The relative stereochemistries of the remaining piperidinones were confirmed by X-ray crystallography (Figure 3.4).

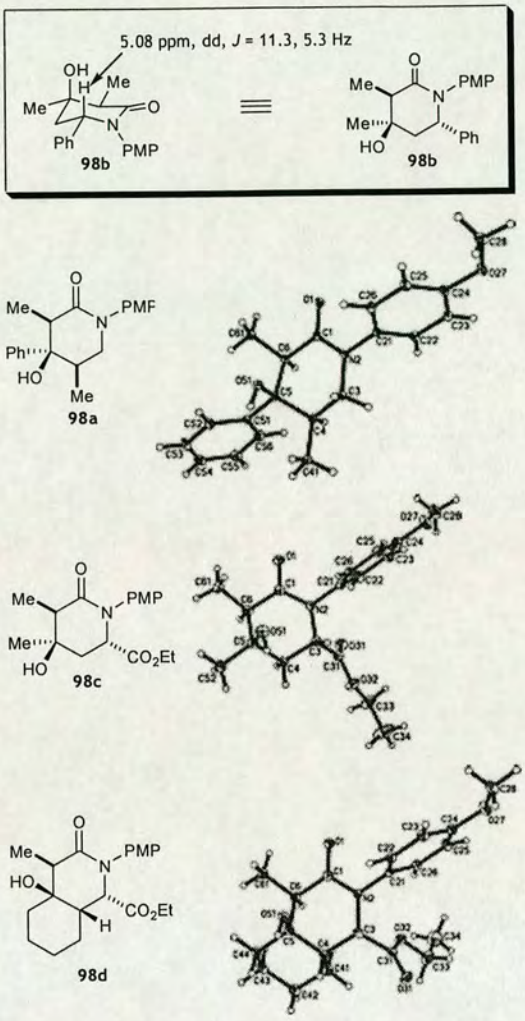
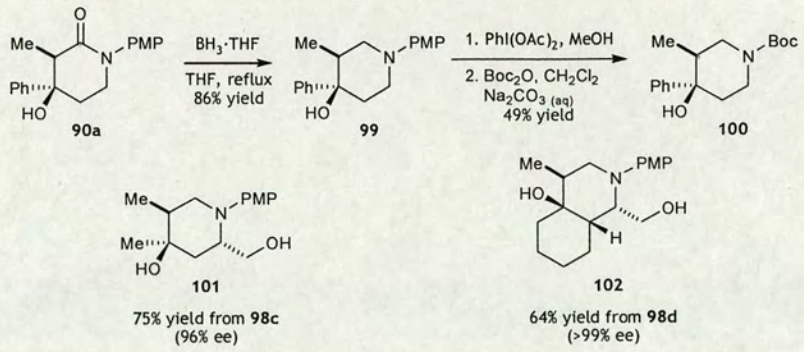


Figure 3.4

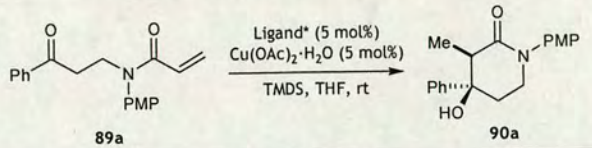
In addition, it is vitally important that the piperidinone products could be further elaborated to gain access to more synthetically desirable materials. To this end, the synthetic utility of the piperinidone products was examined. Reductive removal of the carbonyl group would allow access to the piperidine ring system which is an important structural feature of many natural products and biologically important compounds.[77] For example, exposure of **90a** to borane at reflux provided **99** in good yield. Oxidative removal of the PMP protecting group using $PhI(OAc)_2$[74] followed by *in situ* treatment of the resulting amine with Boc_2O gave **100** in moderate yield over the two steps (Scheme 3.4).



Scheme 3.4

Furthermore, reduction of piperidinones **98c** and **98d** with borane was accompanied by reduction of the esters to give PMP protected piperidines **101** and **102**, respectively. Polyhydroxylated piperidine moieties are of substantial biological importance due to their reported potential to act as glycosidase inhibitors.[78]

Enantioselective carbon–carbon bond forming reactions are invaluable tools in organic synthesis. Therefore, a number of chiral non-racemic ligands were investigated in order to probe a possible asymmetric variant of this methodology (Table 3.5).



89a 90a

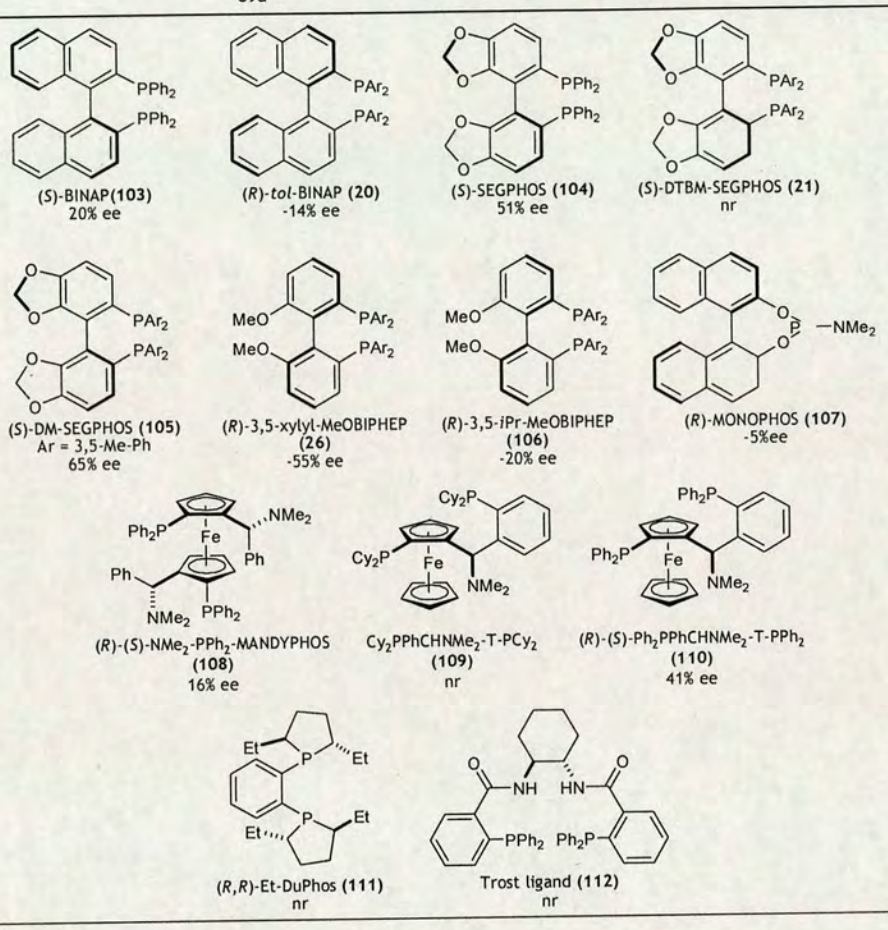
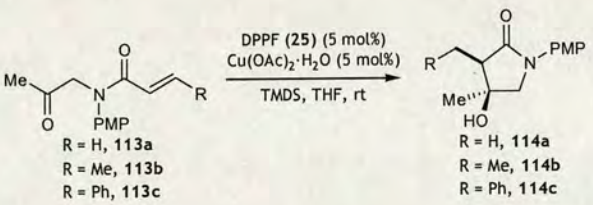


Table 3.5

Of the ligands examined, those based on a biaryl structural motif proved to be the most effective in terms of reactivity, giving product **90a** in the majority of cases. Although the use BINAP-type ligands **(103)** and **(20)** led to efficient cyclisation, the maximum enantiomeric excess of 20% was disappointing. Alternative biaryl-type ligands, for example, SEGPHOS-type **(104)** and **(105)** and BIPHEP-type **(26)** and **(106)** ligands were shown to provide greater levels of stereocontrol, giving the products with enhanced enantiomeric excesses. In the case of (*S*)-SEGPHOS **(104)**, product **90a** was obtained in 51% ee after 24 hrs. Increasing the bulk of the steric

environment around the phosphines by replacing the phenyl groups with 3,5-xylyl groups **(105)** led to a further increase in selectivity, giving the product **90a** in 65% ee. It was envisioned that further increases in the steric bulk of the complexing ligand would lead to further enhancements in the enantiomeric excesses of the observed products. Hence, (*S*)-DTBM-SEGPHOS **(21)** would appear to offer the necessary steric bulk in order to further increase the selectivity of the cyclisation. Unfortunately **(21)** proved to be completely ineffective under these conditions giving only unreacted starting material **89a** after 48 hrs. DPPF **(25)**w as previously shown to be an effective ligand in the non-asymmetric reactions (Table 3.3 and Table 3.4). However, application of chiral non-racemic ferrocene ligands gave only a maximum of 41% ee when (*R*)-(*S*)-$Ph_2PPhCHNMe_2$-T-PPh_2 **(110)** was used as the complexing ligand. Electron-rich phosphine ligands such as: (*R,R*)-Et-DuPhos **(111)**, Trost ligand **(112)**an d $Cy_2PPhCHNMe_2$-T-PCy_2 **(109)**wer e observed to be catalytically inactive for this process.

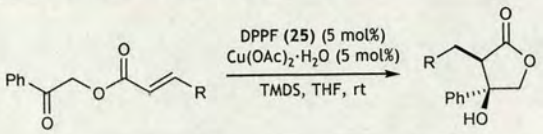
Although the initial programme of research centred on the synthesis of hydroxypiperidin-2-ones, we were interested in applying our optimised methodology to the synthesis of substituted pyrrolidin-2-ones. This γ-lactam motif is prevalent in a number of biologically important natural products, for example, salinosporamide A **(87)** (Figure 3.1). We envisioned that on exposure to our conditions substrates **113a-c** would undergo reductive aldol cyclisation to produce the requisite pyrrolidin-2-ones **114a-c** (eqs 32-34).



R = H, **113a**
R = Me, **113b**
R = Ph, **113c**

R = H, **114a** (32)
R = Me, **114b** (33)
R = Ph, **114c** (34)

However, according to Baldwin's rules this type of 5-(enolendo)-*exo-trig* ring closure is formally disfavoured.[79] Nevertheless previous work within the Lam group has demonstrated that these disfavoured cyclisations occur readily in moderate to good yields in the case of five-membered β-hydroxylactone formation (Table 3.6).[27]



R	%Yield	dr
H	69	>95:5
Me	72	>95:5
^{i}Bu	65	>95:5
$PhCH_2CH_2$	60	>95:5

Table 3.6

Unfortunately, on exposing substrates **113a-c** to our conditions complex mixtures were obtained from which the products of ketone reduction could be observed. An investigation into alternative ligands, silanes and copper salts failed to improve reaction efficiency. Although five-membered β-hydroxylactone formation is facile under these conditions, α,β-unsaturated amide functionalities are less electrophilic compared to the corresponding esters. This may lend itself to slow 1,4-addition of the copper hydride species and therefore, making alternative reaction pathways such as ketone reduction more competitive.

3.2. Conclusions and Future Work

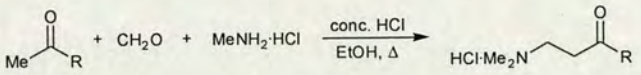
We have developed methodology whereby 4-hydroxypiperidin-2-ones can be constructed in moderate yields and with excellent levels of diastereoselection. However, the synthesis of pyrrolidin-2-ones using this methodology has to date failed to yield any promising results. Furthermore, moderate levels of enantioselection (up to 65% ee) may be achieved by using chiral non-racemic bisphosphine ligands such as (*S*)-DM-SEGPHOS **(105)** in place of DPPF **(25)**i n the synthesis of 4-hydroxypiperidin-2-ones. Finally, by use of L-proline catalysed asymmetric Mannich reactions a selection of highly substituted 4-hydroxypiperidin-2-ones can be synthesised in enantiomerically enriched form from easily attainable and cheap bulk materials. Borane reduction of these products allows entry into the piperidine ring system which is a ubiquitous structural feature in many natural products.[77]

3.3. Experimental

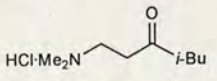
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 was distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Crotonoyl chloride was distilled from CaH_2. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[80] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm, $C_2D_2Cl_4$ at 5.94 ppm, CD_3OD at 3.35 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, $C_2D_2Cl_4$ at 74.2 ppm, CD_3OD at 49.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent

compound. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

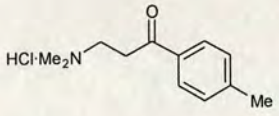
Preparation of β-Dimethylaminoketone Hydrochlorides: General Procedure A



A mixture of the appropriate methyl ketone (1.0 equiv), dimethylamine hydrochloride (1.1 equiv), paraformaldehyde (1.4 equiv), and conc. HCl (5 μL/mmol of methyl ketone) in ethanol (2.0 M with respect to methyl ketone) was heated at reflux until TLC analysis showed the reaction to be complete. The reaction was cooled to room temperature and the ethanol was removed *in vacuo*. EtOAc was added, and the suspension was stirred for 15 min before the solid product was collected by filtration, washed with EtOAc (x 2) and dried under vacuum to leave the β-dimethylaminoketone hydrochloride.

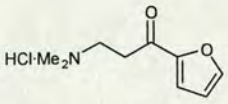


1-Dimethylamino-5-methylhexan-3-one-hydrochloride (115).[81] The title compound was prepared according to general procedure A from 4-methylpentan-2-one (1.25 mL, 10.0 mmol), dimethylamine hydrochloride (906 mg, 11.0 mmol), paraformaldehyde (443 mg, 14.0 mmol) and conc. HCl (50 μL) for a reaction time of 20 h to give a white crystalline solid (700 mg, 36%) which displayed identical spectroscopic data to those previously reported.



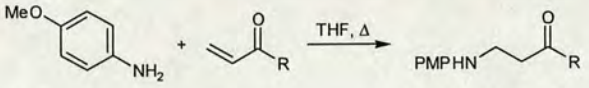
3-Dimethylamino-1-(4-methylphenyl)propan-1-one-hydrochloride (116). The title compound was prepared according to general procedure A from 4'-methylacetophenone (5.6 mL, 40 mmol), dimethylamine hydrochloride (3.62 g, 44.0 mmol), paraformaldehyde (1.77 g, 56.0 mmol) and conc. HCl (0.2 mL) for a reaction time of 36 h to give a white solid (8.03 g, 88%). m.p. 158-160 °C; ^{1}H NMR (360 MHz, CD_3OD) δ 7.99 (2H, d, J = 8.3 Hz, Ar**H**), 7.37 (2H, d, J = 8.3 Hz, Ar**H**), 3.69-3.59 (4H, m, C**H**$_2$C**H**$_2$N), 3.01 (6H, s, N(C**H**$_3$)$_2$), 2.45 (3H, s, C**H**$_3$C$_6$H$_4$); ^{13}C NMR (62.9 MHz, CD_3OD) δ 197.8 (C), 146.1 (C), 134.7 (C), 130.5 (2 x CH), 129.4 (2 x

CH), 54.3 (CH_2), 43.8 (2 x CH_3), 34.2 (CH_2), 21.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{18}NO$ $[M–Cl]^+$: 192.1383, found: 192.1385.

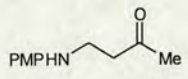


3-Dimethylamino-1-(furan-2-yl)propan-1-one-hydrochloride (117). The title compound was prepared according to general procedure A from 2-furyl methyl ketone (2.22 g, 20.0 mmol), dimethylamine hydrochloride (1.81 g, 22.0 mmol), paraformaldehyde (885 mg, 28.0 mmol) and conc. HCl (0.1 mL) for a reaction time of 20 h to give an off-white crystalline solid (3.00 g, 74%). m.p. 180-182 °C; ^{1}H NMR (360 MHz, CD_3OD) δ 7.89 (1H, dd, J = 1.7, 0.7 Hz, C**H**), 7.52 (1H, dd, J = 3.7, 0.7 Hz, C**H**), 7.34 (1H, dd, J = 3.7, 1.7 Hz, C**H**), 3.61-3.57 (2H, m, C**H**$_2$N), 3.53-3.49 (2H, m, C**H**$_2$$CH_2$N); ^{13}C NMR (62.9 MHz, CD_3OD) δ 186.6 (C), 153.0 (C), 149.2 (CH), 120.0 (CH), 113.8 (CH), 53.7 (CH_2), 43.9 (2 x CH_3), 33.8 (CH_2); HRMS (ES) Exact mass calcd for $C_9H_{14}NO_2$ $[M–Cl]^+$: 168.1019, found: 168.1018.

Preparation of β-Arylaminoketones: General Procedure B

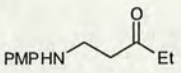


A solution of the appropriate alkyl vinyl ketone (1.2 equiv) and *p*-anisidine (1.0 equiv) in THF (1.0 M with respect to *p*-anisidine) was heated at reflux for 24 h. The mixture was cooled to room temperature and washed with brine. The aqueous layer was extracted with EtOAc (x 2), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the β-aminoketone.



4-(4-Methoxyphenylamino)butan-2-one (118). The title compound was prepared according to general procedure B from methyl vinyl ketone (7.0 mL, 85 mmol) and *p*-anisidine (8.86 g, 71.2 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give an orange/brown oil (13.6 g, 99%), which was judged to be *ca.* 90% pure by ^{1}H NMR spectroscopy. IR (film) 3379 (NH),

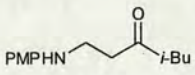
2935, 1711 (C=O), 1513, 1465, 1361, 1237, 1169, 1036, 822 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.78 (2H, d, J = 9.0 Hz, Ar**H**), 6.58 (2H, d, J = 9.0 Hz, Ar**H**), 3.74 (3H, s, OC**H**$_3$), 3.53 (1H, bs, N**H**), 3.34 (2H, t, J = 6.2 Hz, C**H**$_2$N), 2.71 (2H, t, J = 6.2 Hz, C**H**$_2$CH$_2$N), 2.15 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 208.2 (C), 152.1 (C), 141.7 (C), 114.7 (2 x CH), 114.4 (2 x CH), 55.6 (CH_3), 42.5 (CH_2), 39.3 (CH_2), 30.2 (CH_3); LRMS (ES) Mass calculated for $C_{11}H_{16}NO_2$ $[M+H]^+$: 194.1, found: 194.0.



4-(4-Methoxyphenylamino)pentan-3-one (119). The title compound was prepared according to general procedure B from ethyl vinyl ketone (1.47 mL, 14.3 mmol) and *p*-anisidine (1.48 g, 11.9 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a dark orange solid (1.84 g, 75%) that displayed identical spectroscopic data to those previously reported.[82]

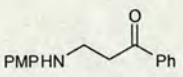
Preparation of β-Arylaminoketones: General Procedure C

A solution of the appropriate β-dimethylaminoketone hydrochloride (1.0 equiv) and the appropriate aniline (1.0 equiv) in 1:1 EtOH/H_2O (1.0 M) was heated at reflux for 24 h. After the mixture was cooled to room temperature, the precipitated solid was collected by filtration, washed with H_2O (x 2) and EtOH (x 2), and dried under vacuum to afford the β-aminoketone.

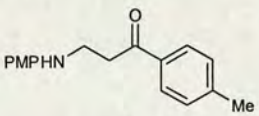


1-(4-Methoxyphenylamino)-5-methylhex-3-one (120). The title compound was prepared according to general procedure C from the dimethylamine hydrochloride **115** (697 mg, 3.60 mmol) and *p*-anisidine (448 mg, 3.60 mmol) to give an orange solid (495 mg, 56%). m.p. 45-47 °C; IR ($CHCl_3$) 3385 (NH), 2956, 1707 (C=O), 1514, 1465, 1367, 1236, 1178, 1038, 820 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.78 (2H, d, J = 9.0 Hz, Ar**H**), 6.59 (2H, d, J = 9.0 Hz, Ar**H**), 3.75 (3H, s, OC**H**$_3$), 3.34 (2H, t, J = 6.1 Hz, C**H**$_2$N), 2.68 (2H, t, J = 6.1 Hz, C**H**$_2$CH$_2$N), 2.29 (2H, d, J = 6.9 Hz, CHC**H**$_2$), 2.19-2.08 (1H, m, C**H**CH$_2$), 0.91 (6H, d, J = 6.6 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 210.1 (C), 152.1 (C),

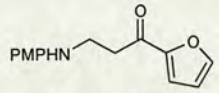
141.8 (C), 114.7 (2 x CH), 114.4 (2 x CH), 55.5 (CH_3), 51.9 (CH_2), 42.0 (CH_2), 39.4 (CH_2), 24.4 (CH), 22.4 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{22}NO_2$ $[M+H]^+$: 236.1645, found: 236.1644.



3-(4-Methoxyphenylamino)-1-phenylpropan-1-one (121). The title compound was prepared according to general procedure C from commercially available 3-(dimethylamino)propiophenone hydrochloride (4.32 g, 20.0 mmol) and *p*-anisidine (2.49 g, 20.0 mmol) to give a light yellow/green crystalline solid (4.80 g, 94%), which displayed identical spectroscopic data to those previously reported.[83]

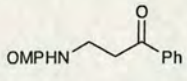


3-(4-Methoxyphenylamino)-1-(4-methylphenyl) propan-1-one (121). The title compound was prepared according to general procedure C from the demethylamine hydrochloride **116** (4.55 g, 20.0 mmol) and *p*-anisidine (2.49 g, 20.0 mmol) to give a yellow/grey crystalline solid (4.13 g, 77%). m.p. 120-121 °C; IR ($CHCl_3$) 3377 (NH), 2856, 1672 (C=O), 1516, 1382, 1288, 1037, 908, 818, 732 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.86 (2H, d, J = 8.5 Hz, Ar**H**), 7.26 (2H, d, J = 8.5 Hz, Ar**H**), 6.81 (2H, d, J = 8.8 Hz, Ar**H**), 6.64 (2H, d, J = 8.8 Hz, Ar**H**), 3.75 (4H, br s, O**CH**$_3$ and N**H**), 3.55 (2H, t, J = 6.2 Hz, C**H**$_2$N), 3.23 (2H, t, J = 6.2 Hz, C**H**$_2$CH$_2$N), 2.42 (3H, s, C**H**$_3$C$_6$H$_4$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.9 (C), 152.1 (C), 144.0 (C), 141.9 (C), 134.1 (C), 129.1 (2 x CH), 128.0 (2 x CH), 114.8 (2 x CH), 114.4 (2 x CH), 55.6 (CH_3), 39.8 (CH_2), 37.4 (CH_2), 21.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{19}NO_2$ $[M+H]^+$: 270.1489, found: 270.1487.



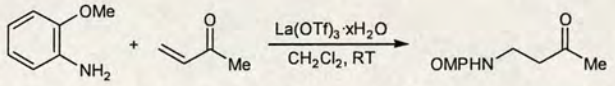
3-(40methoxyphenylamino)-1-(furan-2-yl)propan-1-one (123). The title compound was prepared according to general procedure C from the dimethylamine hydrochloride **117** (2.44 g, 12.0 mmol) and *p*-anisidine (1.49 g, 12.0 mmol) to give a yellow/brown solid (1.10 g, 37%). m.p. 78-79 °C; IR ($CHCl_3$) 3380 (NH), 2832, 1670 (C=O), 1568, 1514, 1467, 1395, 1238, 1034, 822 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.58 (1H, dd, J = 1.7, 0.6 Hz, C**H**), 7.18 (1H, dd, J = 3.6, 0.6 Hz, C**H**), 6.79 (2H, d, J = 8.9 Hz, Ar**H**), 6.62 (2H, d, J =

8.9 Hz, Ar**H**), 6.53 (1H, dd, J = 3.6, 1.7 Hz, C**H**), 3.82 (1H, br s, N**H**), 3.75 (3H, s, OC**H**$_3$), 3.53 (2H, t, J = 6.2 Hz, C**H**$_2$N), 3.12 (2H, t, J = 6.2 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 188.3 (C), 152.6 (C), 152.3 (C), 146.5 (CH), 141.8 (C), 117.3 (CH), 114.9 (2 x CH), 114.5 (2 x CH), 112.3 (CH), 55.7 (CH_3), 39.8 (CH_2), 37.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found: 246.1126.



3-(4-Methoxyphenylamino)-1-furan-2-ylpropan-1-one (124). The title compound was prepared according to general procedure C from commercially available 3-(dimethylamino)propiophenone hydrochloride (2.44 g, 12.0 mmol) and *o*-anisidine (1.49 g, 12.0 mmol) to give a yellow/brown solid (1.10 g, 37%). m.p. 78-79 °C; IR ($CHCl_3$) 3380 (NH), 2832, 1670 (C=O), 1568, 1514, 1467, 1395, 1238, 1034, 822 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.58 (1H, dd, J = 1.7, 0.6 Hz, C**H**), 7.18 (1H, dd, J = 3.6, 0.6 Hz, C**H**), 6.79 (2H, d, J = 8.9 Hz, Ar**H**), 6.62 (2H, d, J = 8.9 Hz, Ar**H**), 6.53 (1H, dd, J = 3.6, 1.7 Hz, C**H**), 3.82 (1H, br s, N**H**), 3.75 (3H, s, OC**H**$_3$), 3.53 (2H, t, J = 6.2 Hz, C**H**$_2$N), 3.12 (2H, t, J = 6.2 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 188.3 (C), 152.6 (C), 152.3 (C), 146.5 (CH), 141.8 (C), 117.3 (CH), 114.9 (2 x CH), 114.5 (2 x CH), 112.3 (CH), 55.7 (CH_3), 39.8 (CH_2), 37.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1125, found: 246.1126.

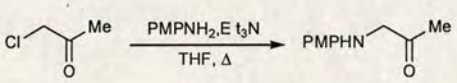
4-(2-Methoxyphenylamino)butan-2-one (125)



A solution of methyl vinyl ketone (4.3 mL, 52 mmol), *o*-anisidine (5.6 mL, 50 mmol) and La(OTf)$_3$·xH$_2$O (1.47 g, 2.50 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 48 h. The mixture was washed with saturated aqueous $NaHCO_3$ solution (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol→60% EtOAc/petrol)

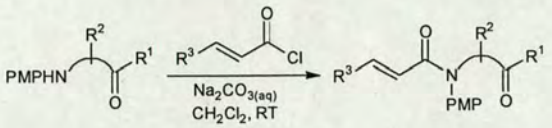
afforded the title compound as a pale pink crystalline solid (5.65 g, 57%). m.p. 40-42 °C; IR ($CHCl_3$) 3408 (NH), 2939, 1713 (C=O), 1602, 1514, 1457, 1247, 1223, 1128, 1028 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.93 (1H, m, ArH), 6.81-6.76 (1H, m, ArH), 6.75-6.68 (1H, m, ArH), 6.66-6.63 (1H, m, ArH), 4.45 (1H, br s, NH), 3.84 (3H, s, OCH_3), 3.44 (2H, t, J = 6.4 Hz, CH_2N), 2.76 (2H, t, J = 6.4 Hz, CH_2CH_2N), 2.16 (3H, s, CH_3C=O); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 207.5 (C), 146.8 (C), 137.4 (C), 121.0 (CH), 116.4 (CH), 109.5 (CH), 109.3 (CH), 55.1 (CH_3), 42.5 (CH_2), 37.8 (CH_2), 29.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{16}NO_2$ $[M+H]^+$: 194.1176, found: 194.1177.

1-(4-Methoxyphenyl)aminopropanone (126)

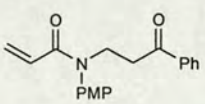


A solution of *p*-anisidine (5.00 g, 40.6 mmol), chloroacetone (3.56 mL, 44.7 mmol) and Et_3N (11.3 mL, 81.2 mmol) in THF (100 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature before the addition of brine (25 mL) and water (25 mL). The aqueous layer was separated and extracted with EtOAc (2 x 30 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) gave the *aminoketone* **126** as a yellow/orange crystalline solid (4.60 g, 68%). m.p. 70-71 °C; IR ($CHCl_3$) 3397 (NH), 2961, 2839, 1715 (C=O), 1511, 1436, 1345, 1254, 1036, 821 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.79 (2H, dm, J = 9.0 Hz, Ar**H**), 6.56 (2H, dm, J = 9.0 Hz, Ar**H**), 4.31 (1H, bs, N**H**), 3.95 (2H, s, C**H**$_2$N), 3.74 (3H, s, OC**H**$_3$), 2.23 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 204.5 (C), 152.2 (C), 141.2 (C), 114.9 (2 x CH), 113.9 (2 x CH), 55.7 (CH_3), 55.1 (CH_2), 27.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 180.1020, found: 180.1032.

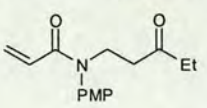
Acylation of *β*-Arylaminoketones: General Procedure D



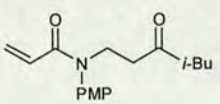
The appropriate α,*β*-unsaturated acid chloride (1.5 equiv) was added dropwise to a vigorously stirred mixture of the appropriate *β*-arylaminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of β-arylaminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of β-arylaminoketone). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclization substrate.



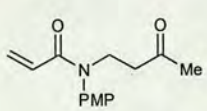
***N*-(4-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl) propenamide (89a)**. The title compound was prepared according to general procedure D from the amine **121** (5.00 g, 19.6 mmol) and acryloyl chloride (2.60 mL, 30.7 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (5.76 g, 95%). m.p. 51-53 °C; IR ($CHCl_3$) 2933, 1681 (C=O), 1655 (C=O), 1614, 1510, 1446, 1411, 1249, 1210, 1180 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.57 (1H, m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 7.11-7.06 (2H, m, Ar**H**), 6.93-6.89 (2H, m, Ar**H**), 6.36 (1H, dd, J = 16.8, 2.0 Hz, =C**H**), 6.03 (1H, dd, J = 16.8, 10.3 Hz, =C**H**), 5.52 (1H, dd, J = 10.3, 2.0 Hz, =C**H**), 4.14 (2H, t, J = 7.5 Hz, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$), 3.34 (2H, t, J = 7.5 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.4 (C), 165.9 (C), 159.0 (C), 136.5 (C), 134.5 (C), 133.2 (CH), 129.1 (2 x CH), 128.5 (3 x CH), 128.0 (2 x CH), 127.4 (CH_2), 114.7 (2 x CH), 55.4 (CH_3), 46.1 (CH_2), 36.6 (CH_2); HRMS (FAB) Exact mass calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found: 310.1442.



***N*-(4-Methoxyphenyl)-*N*-(3-oxopentyl) propenamide (89b).** The title compound was prepared according to general procedure D from the amine **119** (500 mg, 2.41 mmol) and acryloyl chloride (305 μL, 3.60 mmol) for a reaction time of 20 h and purified by column chromatography (EtOAc) to give an orange/brown solid (620 mg, 98%). m.p. 43-44 °C; IR ($CHCl_3$) 2938, 1712 (C=O), 1654 (C=O), 1615, 1510, 1412, 1249, 1182, 1031, 795 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.06 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.91 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.33 (1H, dd, *J* = 16.8, 2.0 Hz, =C**H**), 5.99 (1H, dd, *J* = 16.8, 10.3 Hz, =C**H**), 5.50 (1H, dd, *J* = 10.3, 2.0 Hz, =C**H**), 4.00 (2H, t, *J* = 7.5 Hz, C$\mathbf{H}_2$N), 3.83 (3H, s, OC$\mathbf{H}_3$), 2.74 (2H, t, *J* = 7.5 Hz, C$\mathbf{H}_2$$CH_2$N), 2.43 (2H, q, *J* = 7.3 Hz, C$\mathbf{H}_2$$CH_3$), 1.02 (3H, t, *J* = 7.3 Hz, CH_2C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.7 (C), 165.8 (C), 159.0 (C), 134.3 (C), 129.2 (2 x CH), 128.5 (CH), 127.4 (CH_2), 114.7 (2 x CH), 55.5 (CH_3), 45.2 (CH_2), 40.1 (CH_2), 36.0 (CH_2), 7.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1441.

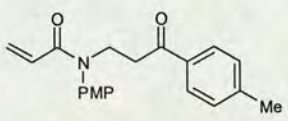


N-(4-Methoxyphenyl)-N-(5-methyl-3-oxohexyl) propenamide (89c). The title compound was prepared according to general procedure D from the amine **120** (500 mg, 2.12 mmol) and acryloyl chloride (260 μL, 3.07 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give an orange oil (400 mg, 65%). IR (film) 2956, 1710 (C=O), 1657 (C=O), 1616, 1511, 1411, 1249, 1181, 1032, 839 cm-1; 1H NMR (360 MHz, CDCl3) δ 7.05 (2H, d, J = 8.9 Hz, ArH), 6.91 (2H, d, J = 8.9 Hz, ArH), 6.38 (1H, dd, J = 16.8, 2.0 Hz, =CH), 5.98 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.49 (1H, dd, J = 10.3, 2.0 Hz, =CH), 3.98 (2H, t, J = 7.5 Hz, CH2N), 2.72 (2H, d, J = 6.9 Hz, (CH3)2CHCH2), 2.15-2.03 (1H, m, (CH3)2CH), 0.88 (6H, d, J = 6.6 Hz, (CH3)2CH); 13C NMR (62.9 MHz, CDCl3) δ 208.9 (C), 165.7 (C), 158.9 (C), 134.3 (C), 129.2 (2 x CH), 128.5 (CH), 127.3 (CH2), 114.7 (2 x CH), 55.4 (CH3), 51.8 (CH2), 45.0 (CH2), 40.8 (CH2), 24.3 (CH), 22.5 (2 x CH3); HRMS (ES) Exact mass calcd for C17H24NO3 [M+H]+: 290.1751, found: 290.1752.

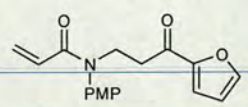


***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl) propenamide (89d).** The title compound was prepared according to general procedure D

from the amine **118** (1.46 g, 7.56 mmol) and acryloyl chloride (950 μL, 11.2 mmol) for a reaction time of 1.5 h and purified by column chromatography (50% EtOAc/petrol) to give a light brown oil (970 mg, 52%). IR (film) 2956, 1713 (C=O), 1656 (C=O), 1618, 1512, 1412, 1249, 1169, 1030, 838 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.02 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.87 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.27 (1H, dd, *J* = 16.8, 2.0 Hz, =C**H**), 5.94 (1H, dd, *J* = 16.8, 10.3 Hz, =C**H**), 5.44 (1H, dd, *J* = 10.3, 2.0 Hz, =C**H**), 3.94 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$N), 3.78 (3H, s, OC$\mathbf{H}_3$), 2.71 (3H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$CH$_2$N), 2.08 (3H, s, C$\mathbf{H}_3$C=O); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 206.8 (C), 165.6 (C), 158.9 (C), 134.1 (C), 129.1 (2 x CH), 128.4 (CH), 127.3 (CH_2), 114.6 (2 x CH), 55.3 (CH_3), 44.9 (CH_2), 41.2 (CH_2), 29.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281, found: 248.1288.

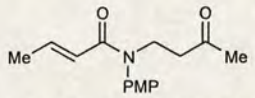


***N*-(4-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl) propenamide (89e)**. The title compound was prepared according to general procedure D from the amine **122** (5.00 g, 19.6 mmol) and acryloyl chloride (2.60 mL, 30.7 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (5.76 g, 95%). m.p. 51-53 °C; IR ($CHCl_3$) 2933, 1681 (C=O), 1655 (C=O), 1614, 1510, 1446, 1411, 1249, 1210, 1180 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.96-7.93 (2H, m, Ar**H**), 7.57 (1H, m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 7.11-7.06 (2H, m, Ar**H**), 6.93-6.89 (2H, m, Ar**H**), 6.36 (1H, dd, *J* = 16.8, 2.0 Hz, =C**H**), 6.03 (1H, dd, *J* = 16.8, 10.3 Hz, =C**H**), 5.52 (1H, dd, *J* = 10.3, 2.0 Hz, =C**H**), 4.14 (2H, t, *J* = 7.5 Hz, C$\mathbf{H}_2$N), 3.81 (3H, s, OC$\mathbf{H}_3$), 3.34 (2H, t, *J* = 7.5 Hz, C$\mathbf{H}_2$CH$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.4 (C), 165.9 (C), 159.0 (C), 136.5 (C), 134.5 (C), 133.2 (CH), 129.1 (2 x CH), 128.5 (3 x CH), 128.0 (2 x CH), 127.4 (CH_2), 114.7 (2 x CH), 55.4 (CH_3), 46.1 (CH_2), 36.6 (CH_2); HRMS (FAB) Exact mass calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found: 310.1442.

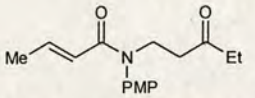


***N*-(4-Methoxyphenyl)-*N*-[3-(furan-2-yl)-3-oxopropyl] propenamide (89f)**. The title compound was prepared according to general procedure D from the amine **123** (1.00 g, 4.08 mmol) and acryloyl chloride (509 μL, 6.02 mmol) for a reaction time of 20 h and purified by

column chromatography (30% EtOAc/petrol) to give a white solid. m.p. 93-94 °C; IR ($CHCl_3$) 2937, 1656 (C=O), 1614, 1569, 1510, 1469, 1411, 1249, 1182, 1029 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.57 (1H, dd, J = 1.7, 0.7 Hz, C**H**), 7.25 (1H, dd, J = 3.6, 0.7 Hz, C**H**), 7.07 (1H, d, J = 9.0 Hz, Ar**H**), 6.90 (1H, d, J = 9.0 Hz, Ar**H**), 6.52 (1H, dd, J = 3.6, 1.7 Hz, C**H**), 6.34 (1H, dd, J = 16.8, 2.0 Hz, =C**H**), 6.01 (1H, dd, J = 16.8, 10.3 Hz, =C**H**), 5.50 (1H, dd, J = 10.3, 2.0 Hz, =C**H**), 4.12 (2H, t, J = 7.5 Hz, C**H**$_2$N), 3.82 (3H, s, OC**H**$_3$), 3.18 (2H, t, J = 7.5 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 187.1 (C), 165.9 (C), 159.0 (C), 152.3 (C), 146.5 (CH), 134.4 (C), 129.2 (2 x CH), 128.5 (CH), 127.5 (CH_2), 117.7 (CH), 114.7 (2 x CH), 112.2 (CH), 55.5 (CH_3), 45.9 (CH_2), 36.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{17}H_{18}NO_4$ $[M+H]^+$: 300.1230, found: 300.1229.

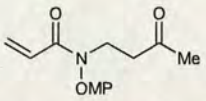


***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-but-2-enamide (89g)**. The title compound was prepared according to general procedure D from the amine **118** (970 mg, 5.02 mmol) and crotonoyl chloride (718 μL, 7.50 mmol) for a reaction time of 2 h and purified by column chromatography (50% EtOAc/petrol) to give a light brown oil (1.01 g, 77%). IR (film) 2936, 1713 (C=O), 1664 (C=O), 1627, 1511, 1444, 1292, 1249, 1168, 1031 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.06 (2H, d, J = 9.0 Hz, Ar**H**), 6.94-6.84 (1H, m, =C**H**), 6.92 (2H, d, J = 9.0 Hz, Ar**H**), 5.66 (1H, dq, J = 15.1, 1.7 Hz, =C**H**), 3.98 (2H, t, J = 7.4 Hz, C**H**$_2$N), 3.85 (3H, s, OC**H**$_3$), 2.14 (3H, s, C**H**$_3$C=O), 1.73 (3H, dd, J =6.9, 1.7 Hz, C**H**$_3$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 207.0 (C), 166.1 (C), 158.8 (C), 141.2 (CH), 134.5 (C), 129.2 (2 x CH), 122.6 (CH), 114.6 (2 x CH), 55.4 (CH_3), 44.9 (CH_2), 41.5 (CH_2), 29.9 (CH_3), 17.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1437.

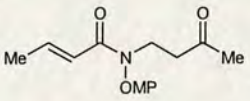


***N*-(4-Methoxyphenyl)-*N*-(3-oxopentyl)-(*E*)-but-2-enamide (89h)**. The title compound was prepared according to general procedure D from the amine **119** (500 mg, 2.41 mmol) and crotonoyl chloride (345 μL, 3.60 mmol) for a reaction time of 20 h and purified by column chromatography (EtOAc) to give an orange oil (645 mg, 97%). IR (film) 2938, 1712 (C=O), 1665 (C=O), 1627, 1510, 1445, 1292, 1249, 1182, 1032 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$)

δ 7.05 (2H, d, J = 9.0 Hz, Ar**H**), 6.91 (2H, d, J = 9.0 Hz, Ar**H**), 6.91-6.83 (1H, m, =C**H**), 5.65 (1H, dq, J = 15.1, 1.6 Hz, =C**H**), 3.96 (2H, t, J = 7.4 Hz, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 2.72 (2H, t, J = 7.5 Hz, C**H**$_2$CH$_2$N), 2.41 (2H, q, J = 7.3 Hz, C**H**$_2$CH$_3$), 1.71 (3H, dd, J = 6.9, 1.6 Hz, C**H**$_3$CH=), 1.01 (3H, t, J = 7.3 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 209.8 (C), 166.2 (C), 158.8 (C), 141.3 (CH), 134.7 (C), 129.3 (2 x CH), 122.7 (CH), 114.6 (2 x CH), 55.5 (CH_3), 45.1 (CH_2), 40.2 (CH_2), 36.0 (CH_2), 17.9 (CH_3), 7.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1594, found: 276.1594.

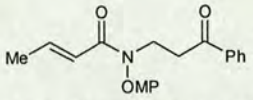


***N*-(2-Methoxyphenyl)-*N*-(3-oxobutyl)propenamide (89i)**. The title compound was prepared according to general procedure D from the amine **125** (483 mg, 2.50 mmol) and acryloyl chloride (317 μL, 3.75 mmol) for a reaction time of 20 h and purified by column chromatography (50% EtOAc/petrol→EtOAc) to give a light orange oil (610 mg, 99%). IR (film) 2944, 1713 (C=O), 1657 (C=O), 1618, 1595, 1500, 1415, 1267, 1024, 756 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.29-7.24 (1H, m, Ar**H**), 7.02 (1H, dd, J = 8.0, 1.8 Hz, Ar**H**), 6.92-6.88 (2H, m, Ar**H**), 6.24 (1H, dd, J = 16.8, 2.1 Hz, =C**H**), 5.85 (1H, dd, J = 16.8, 10.3 Hz, =C**H**), 5.38 (1H, dd, J= 10.3, 2.1 Hz, =C**H**), 3.99-3.91 (1H, m, C**H**$_2$N), 3.82-3.74 (1H, m, C**H**$_2$N), 3.72 (3H, s, OC**H**$_3$), 2.71 (2H, t, J = 7.4 Hz, C**H**$_2$CH$_2$N), 2.04 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 207.1 (C), 166.0 (C), 155.1 (C), 130.0 (C), 129.8 (CH), 129.5 (CH), 128.2 (CH), 127.0 (CH_2), 120.8 (CH), 111.7 (CH), 55.3 (CH_3), 43.9 (CH_2), 41.3 (CH_2), 29.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281, found: 248.1281.

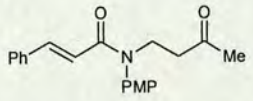


***N*-(2-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-but-2-enamide (89j)**. The title compound was prepared according to general procedure D from the amine **125** (483 mg, 2.50 mmol) and crotonoyl chloride (360 μL, 3.76 mmol) for a reaction time of 20 h and purified by column chromatography (50% EtOAc/petrol→EtOAc) to give a yellow oil (653 mg, >99%). IR (film) 2942, 1713 (C=O), 1666 (C=O), 1629, 1500, 1443, 1398, 1369, 1291, 1244 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36-7.31 (1H, m, Ar**H**), 7.08-7.05 (1H, m, Ar**H**), 6.98-6.94 (2H, m, Ar**H**), 6.90-6.82 (1H, m, =C**H**), 5.61-5.56 (1H, m,

=C**H**), 4.07-3.99 (1H, m, C**H**$_2$N), 3.79 (3H, s, OC**H**$_3$), 2.84-2.69 (2H, m, C**H**$_2$CH$_2$N), 2.10 (3H, s, C**H**$_3$C=O), 1.68 (3H, app ddd, J = 6.9, 1.7, 0.9 Hz, C**H**$_3$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 207.3 (C), 166.3 (C), 155.2 (C), 140.8 (CH), 130.3 (C), 130.0 (CH), 129.3 (CH), 122.3 (CH), 120.7 (CH), 111.8 (CH), 55.3 (CH_3), 43.8 (CH_2), 41.5 (CH_2), 29.9 (CH_3), 17.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1437.



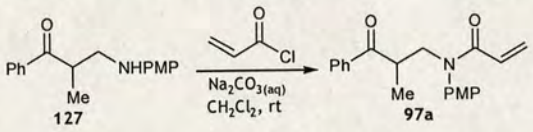
***N*-(2-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)-(*E*)-but-2-enamide (89k).** The title compound was prepared according to general procedure D from the amine **124** (1.03 g, 4.03 mmol) and crotonoyl chloride (575 μL, 6.00 mmol) for a reaction time of 20 h and purified by column chromatography (50% EtOAc/petrol) to give an off-white solid (830 mg, 64%). m.p. 118-119 °C; IR ($CHCl_3$) 2940, 1682 (C=O), 1666 (C=O), 1627, 1596, 1499, 1447, 1397, 1243, 1024 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.98-7.96 (2H, m, Ar**H**), 7.56-7.52 (1H, m, Ar**H**), 7.47-7.42 (2H, m, Ar**H**), 7.36-7.31 (1H, m, Ar**H**), 7.13-7.10 (1H, m, Ar**H**), 7.00-6.88 (3H, m, Ar**H** and =C**H**), 5.67-5.62 (1H, m, =C**H**), 4.18-4.10 (1H, m, C**H**$_2$N), 4.05-3.97 (1H, m, C**H**$_2$N), 3.75 (3H, s, OC**H**$_3$), 3.47-3.39 (1H, m, C**H**$_2$CH$_2$N), 3.36-3.27 (1H, m, C**H**$_2$CH$_2$N), 1.72 (3H, dd, J = 6.9, 1.7 Hz, C**H**$_3$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.8 (C), 166.6 (C), 155.3 (C), 141.0 (CH), 136.7 (C), 133.0 (CH), 130.8 (C), 130.0 (CH), 129.4 (CH), 128.5 (2 x CH), 128.1 (2 x CH), 122.5 (CH), 120.8 (CH), 111.8 (CH), 55.4 (CH_3), 45.1 (CH_2), 37.0 (CH_2), 17.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found: 324.1594.



***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenoate (89l).** The title compound was prepared according to General Procedure D from the amine **118** (2.00 g, 10.3 mmol) and cinnamoyl chloride (2.10 g, 12.4 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→40% EtOAc/petrol) followed by recrystallization from EtOAc/petrol to give a colorless crystalline solid (1.84 g, 55%). m.p. 85-86 °C; IR ($CHCl_3$) 2955, 1713 (C=O), 1654 (C=O), 1615, 1510, 1394, 1249, 1183, 1030, 765 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.63 (1H, d,

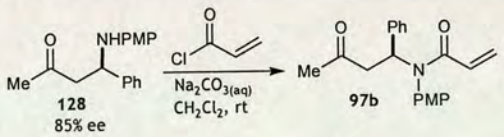
J = 15.6 Hz, PhC**H**=), 7.29-7.26 (5H, m, Ar**H**), 7.11 (2H, dm, J = 8.9 Hz, Ar**H**), 6.93 (2H, dm, J = 8.9 Hz, Ar**H**), 6.26 (1H, d, J = 15.6 Hz, PhCH=C**H**), 4.03 (2H, t, J = 7.4 Hz, C**H**$_2$N), 3.84 (3H, s, OC**H**$_3$), 2.78 (2H, t, J = 7.4 Hz, C**H**$_2$CH$_2$N), 2.14 (3H, s, C**H**$_3$C=O); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 207.0 (C), 166.2 (C), 158.9 (C), 141.8 (CH), 135.1 (C), 134.5 (C), 129.5 (CH), 129.3 (2 x CH), 128.6 (2 x CH), 127.8 (2 x CH), 118.7 (CH), 114.8 (2 x CH), 55.5 (CH_3), 45.2 (CH_2), 41.5 (CH_2), 30.0 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1595, found: 324.1599.

_N_-(4-Methoxyphenyl)-_N_-[2-methyl-3-oxo-3-phenylpropyl]propenamide (97a)



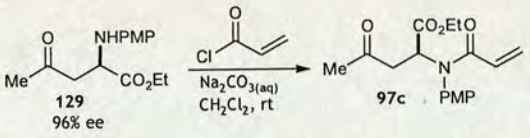
The title compound was prepared according to general procedure D from the amine **127**[83] (808 mg, 3.00 mmol) for a reaction time of 16 h and purified by column chromatography (20 % EtOAc/petrol) to give a colorless oil (807 mg, 83 %). IR (film) 2934, 1681 (C=O), 1658 (C=O), 1617, 1510, 1446, 1409, 1248, 1031, 973 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.92-7.90 (2H, m, ArH), 7.56-7.52 (1H, m, ArH), 7.46-7.41 (2H, m, ArH), 6.93 (2H, d, J = 8.7 Hz, ArH), 6.82 (2H, d, J = 8.7 Hz, ArH), 6.34 (1H, dd, J = 16.8, 2.0 Hz, =CH), 5.98 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.48 (1H, dd, J = 10.3, 2.0 Hz, =CH), 4.17-3.95 (3H, m, CHC**H**$_2$N), 3.79 (3H, s, OC**H**$_3$), 1.22 (3H, d, J = 6.9 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.6 (C), 166.4 (C), 158.7 (C), 136.3 (C), 135.1 (C), 133.1 (CH), 129.0 (2 x CH), 128.7 (CH), 128.6 (2 x CH), 128.3 (2 x CH), 127.4 (CH_2), 114.5 (2 x CH), 55.4 (CH_3), 53.4 (CH_2), 39.6 (CH), 16.0 (CH_3); HRMS (ES) Exact mass calcd for CHNO $[M+H]^+$: , found .

_N_-(4-Methoxyphenyl)-_N_-[*S*)-3-oxo-1-phenylbutyl]propenamide (97b)



The title compound was prepared according to general procedure D from the amine **128** (350 mg, 1.30 mmol, prepared in 85% ee according to a literature procedure)[84] and acryloyl chloride (165 μL, 1.95 mmol) for a reaction time of 5 h and purified by column chromatography (30% EtOAc/petrol) to give a colourless viscous oil (390 mg, 93%). $[\alpha]_D^{22}$ +20.9 (*c* 1.05, $CHCl_3$); IR (film) 2959, 1715 (C=O), 1653 (C=O), 1614, 1510, 1406, 1252, 1171, 1031, 834 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.26-7.24 (3H, m, Ar**H**), 7.20-7.17 (2H, m, Ar**H**), 6.77 (4H, br s, Ar**H**), 6.50 (1H, dd, *J* = 9.1, 6.4 Hz, C**H**N), 6.35 (1H, dd, *J* = 16.8, 2.0 Hz, =C**H**), 5.81 (1H, dd, *J* = 16.8, 10.3 Hz, =C**H**), 5.46 (1H, dd, *J* = 10.3, 2.0 Hz, =C**H**), 3.79 (3H, s, OC**H**$_3$), 3.16 (1H, dd, *J* = 15.7, 9.1 Hz, C**H**$_2$CHN), 2.96 (1H, dd, *J* = 15.7, 6.4 Hz, C**H**$_2$CHN), 2.24 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.8 (C), 165.6 (C), 159.0 (C), 138.8 (C), 131.1 (2 x CH), 130.5 (C), 128.8 (CH), 128.1 (2 x CH), 128.0 (2 x CH), 127.6 (CH), 127.4 (CH_2), 113.9 (2 x CH), 55.1 (CH), 54.5 (CH_3), 45.3 (CH_2), 29.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{22}NO_3$ $[M+H]^+$: 324.1594, found: 324.1590.

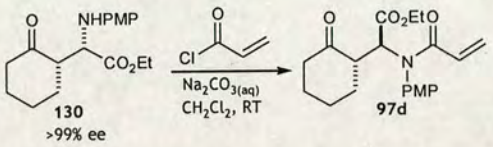
Ethyl (2*S*)-2-*N*-(4-methoxyphenyl)acrylamido-4-oxopentanoate (97c)



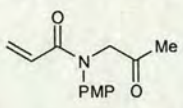
The title compound was prepared according to general procedure D from the amine **129** (950 mg, 3.58 mmol, prepared in 96% ee according to a literature procedure)[84] and acryloyl chloride (457 μL, 5.40 mmol) for a reaction time of 1 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow solid (762 mg, 66%). m.p. 74-76 °C; $[\alpha]_D^{22}$ –41.9 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 2981, 1739 (C=O), 1721 (C=O), 1659 (C=O), 1619, 1511, 1411, 1249, 1030, 841 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.19 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.90 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.33 (1H, dd, *J* = 16.8, 2.0 Hz, =C**H**), 5.96 (1H, dd, *J* = 16.8, 10.3 Hz, =C**H**), 5.51 (1H, dd, *J* = 10.3, 2.0 Hz, =C**H**), 4.96 (1H, app t, *J* = 6.5 Hz, C**H**CO_2Et), 4.26-4.16 (2H, m, CO_2C**H**$_2$CH$_3$), 3.83 (3H, s, OC**H**$_3$), 3.51 (1H, dd, *J* = 17.7, 6.9 Hz, C**H**$_2$CHCO$_2$Et), 2.87 (1H, dd, *J* = 17.7, 6.1 Hz, C**H**$_2$CHCO$_2$Et), 2.16 (3H, s,

CH_3C=O), 1.27 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.3 (C), 170.1 (C), 165.9 (C), 159.2 (C), 134.0 (C), 129.6 (2 x CH), 128.1 (CH), 128.0 (CH_2), 114.5 (2 x CH), 61.5 (CH_2), 58.8 (CH), 55.4 (CH_3), 43.2 (CH_2), 30.1 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{21}NO_5$ $[M+H]^+$: 320.1492, found: 320.1493.

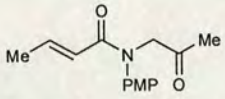
Ethyl(2*S*,1'*S*)-2-*N*-(4-methoxyphenyl)acrylamido-2-(-2'-oxocyclohex-1'-yl)acetate (97d)



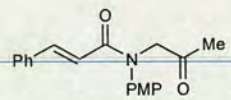
The title compound was prepared according to general procedure D from the amine **130** (1.07 g, 3.50 mmol, prepared in >99% ee according to a literature procedure)[84] and acryloyl chloride (444 μL, 5.25 mmol) for a reaction time of 2 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (1.21 g, 96%). m.p. 132-134 °C; $[\alpha]_D^{22}$ –187 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2939, 1741 (C=O), 1712 (C=O), 1659 (C=O), 1619, 1510, 1411, 1250, 1182, 1030 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.19 (2H, br s, ArH), 6.90 (2H, d, J = 9.1 Hz, ArH), 6.34 (1H, dd, J = 16.8, 2.0 Hz, =CH), 6.01 (1H, dd, J = 16.8, 10.3 Hz, =CH), 5.53 (1H, dd, J = 10.3, 2.0 Hz, =CH), 4.84 (1H, d, J = 6.9 Hz, $CHCO_2Et$), 4.18 (2H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 3.83 (3H, s, OCH_3), 3.60 (1H, ddd, J = 14.0, 9.6, 5.4 Hz, $CHCHCO_2Et$), 2.57-2.37 (2H, m, $(CH_2)_4$), 2.24-2.11 (2H, m, $(CH_2)_4$), 1.95-1.92 (1H, m, $(CH_2)_4$), 1.84-1.57 (2H, m, $(CH_2)_4$), 1.49-1.39 (1H, m, $(CH_2)_4$), 1.25 (3H, t, J = 7.1 Hz, $CO_2CH_2CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 211.2 (C), 169.7 (C), 166.2 (C), 159.0 (C), 135.1 (C), 129.2 (2 x CH), 128.2 (CH_2), 127.9 (CH), 114.6 (2 x CH), 62.3 (CH), 61.2 (CH_2), 55.4 (CH_3), 49.9 (CH), 42.3 (CH_2), 31.7 (CH_2), 28.7 (CH_2), 25.3 (CH_2), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1805, found: 360.1805.



***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)propenamide (113a).** The title compound was prepared according to general procedure D from the amine **126** (1.07 g, 6.00 mmol) and acryloyl chloride (762 μL, 9.00 mmol) for a reaction time of 2.5 h and purified by column chromatography (30% EtOAc/petrol→60% EtOAc/petrol) to give a beige solid (1.21 g, 87%). m.p. 48-51 °C; IR ($CHCl_3$) 2960, 1732 (C=O), 1652 (C=O), 1618, 1512, 1427, 1250, 1172, 1030, 843 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.21 (2H, dm, J = 8.9 Hz, Ar**H**), 6.88 (2H, dm, J = 8.9 Hz, Ar**H**), 6.35 (1H, dd, J = 16.8, 2.0 Hz, C**H**$_2$=), 6.10 (1H, dd, J = 16.8, 10.3 Hz, CH_2=C**H**), 5.54 (1H, dd, J = 10.3, 2.0 Hz, C**H**$_2$=), 4.47 (2H, s, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$), 2.18 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.3 (C), 165.9 (C), 159.1 (C), 135.0 (C), 129.2 (2 x CH), 128.1 (CH_2), 127.7 (CH), 114.6 (2 x CH), 59.7 (CH_2), 55.4 (CH_3), 27.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{16}NO_3$ $[M+H]^+$: 234.1125, found: 234.1125.



***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-but-2-enamide (113b).** The title compound was prepared according to General Procedure D from the amine **126** (1.05 g, 5.80 mmol) and crotonoyl chloride (834 μL, 8.70 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol) to give a yellow oil (921 mg, 64%). IR (film) 2915, 1731 (C=O), 1665 (C=O), 1628, 1513, 1250, 1030, 967, 842, 686 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 9.0 Hz, Ar**H**), 6.92 (1H, app q, J = 6.9 Hz, CH_3C**H**=), 6.87 (2H, d, J = 9.0 Hz, Ar**H**), 5.77 (1H, dq, J = 15.1, 1.7 Hz, C**H**C=O), 4.43 (2H, s, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 2.15 (3H, s, C**H**$_3$C=O), 1.72 (3H, dd, J = 6.9, 1.7 Hz, C**H**$_3$CH=); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 202.6 (C), 166.2 (C), 158.9 (C), 142.0 (CH), 135.3 (C), 129.2 (2 x CH), 121.8 (CH), 114.5 (2 x CH), 59.6 (CH_2), 55.4 (CH_3), 27.1 (CH_3), 17.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281, found: 248.1279.



***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-phenylpropenamide (113c).** The title compound was prepared according to General Procedure D from the amine **126** (1.07 g, 6.00 mmol) and cinnamoyl chloride (1.50 g, 9.00 mmol) for a reaction time of 2.5 h and purified by

column chromatography (30% EtOAc/petrol→60% EtOAc/petrol) followed by recrystallization (EtOAc/petrol) to give a beige solid (590 mg, 32%). m.p. 115-117 °C; IR ($CHCl_3$) 2918, 1731 (C=O), 1654 (C=O), 1616, 1511, 1378, 1250, 1214, 1171, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.67 (1H, d, J = 15.6 Hz, PhC**H**=), 7.67-7.29 (7H, m, Ar**H**), 6.92 (2H, dm, J = 8.8 Hz, Ar**H**), 6.39 (1H, d, J = 15.6 Hz, PhCH=C**H**), 4.52 (2H, s, C**H**$_2$N), 3.34 (3H, s, OC**H**$_3$), 2.20 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.5 (C), 159.0 (C), 142.4 (CH), 135.1 (C), 135.0 (C), 129.5 (CH), 129.2 (2 x CH), 128.6 (2 x CH), 127.8 (2 x CH), 117.8 (CH), 114.6 (2 x CH), 59.8 (CH_2), 55.4 (CH_3), 27.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found: 310.1437.

Copper-Catalysed Reductive Aldol Cyclisations

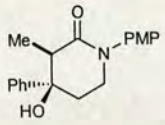
General Procedure E: (1 mmol Scale)

A solution of $Cu(OAc)_2 \cdot H_2O$ (10.0 mg, 0.05 mmol) and DPPF **(25)** (28.6 mg, 0.05 mmol) in THF (2 mL) was stirred for 15 min before TMDS (182 μL, 1.00 mmol) was added. The initially green solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (1.00 mmol) in THF (2 mL + 1 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclised product.

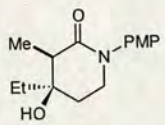
General Procedure F: (0.2 mmol Scale)

A solution of $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol) and DPPF **(25)** (5.7 mg, 0.01 mmol) in THF (1 mL) was stirred for 15 min before TMDS (36 μL, 0.20 mmol) was added. The initially green solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (0.20 mmol) in THF (0.5 mL + 0.5 mL rinse)

was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (0.5 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclised product.

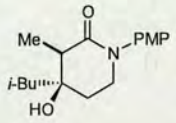


(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpiperidin-2-one (90a). The title compound was prepared according to general procedure F from **89a** (62 mg, 0.20 mmol) for a reaction time of 21 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (43 mg, 69%). Slow evaporation of a $CDCl_3$ solution of **90a** was found to give colourless crystals suitable for X-ray diffraction. m.p. 159-161 °C; IR ($CHCl_3$) 3389 (OH), 2940, 1629 (C=O), 1605, 1511, 1444, 1335, 1299, 1245,1034 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49-7.46 (2H, m, Ar**H**), 7.43-7.39 (2H, m, Ar**H**), 7.33-7.29 (1H, m, Ar**H**), 7.19 (2H, d, J = 8.5 Hz, Ar**H**), 6.91 (2H, d, J = 8.5 Hz, Ar**H**), 4.06-3.98 (1H, m, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.48-3.44 (1H, m, C**H**$_2$N), 3.02 (1H, q, J = 7.1 Hz, CH$_3$C**H**), 2.48-2.39 (1H, m, C**H**$_2$CH$_2$N), 2.30 (1H, br s, O**H**), 2.12-2.08 (1H, m, C**H**$_2$CH$_2$N), 1.12 (3H, d, J = 7.1 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.0 (C), 158.0 (C), 145.8 (C), 136.2 (C), 128.5 (2 x CH), 127.4 (2 x CH), 127.2 (CH), 124.5 (2 x CH), 114.3 (2 x CH), 74.6 (C), 55.4 (CH_3), 47.6 (CH_2), 46.5 (CH), 36.7 (CH_2), 10.0 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1594, found: 312.1599.

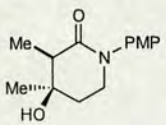


(±)-(3*R*,4*R*)-4-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (90b). The title compound was prepared according to general procedure E from **89b** (261 mg, 1.00 mmol) for a reaction time of 5.5 h and purified by column chromatography (80% EtOAc/petrol→EtOAc) to give a white solid (161 mg, 61%). m.p. 132-134 °C; IR ($CHCl_3$) 3410 (OH), 2962, 1631 (C=O), 1604, 1511, 1331, 1297, 1244, 1034, 830 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.15 (2H, d, J = 9.0 Hz, Ar**H**), 6.90 (2H, d, J =

9.0 Hz, Ar**H**), 3.86 (1H, ddd, J = 12.0, 8.3, 6.7 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.46 (1H, ddd, J = 12.0, 10.2, 5.2 Hz, C**H**$_2$N), 2.54 (1H, q, J = 7.2 Hz, CH$_3$C**H**), 2.00-1.96 (2H, m, C**H**$_2$CH$_2$N), 1.70-1.61 (3H, m, CH$_3$C**H**$_2$ and O**H**), 1.29 (3H, d, J = 7.2 Hz, C**H**$_3$CH), 0.97 (3H, t, J = 7.5 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.3 (C), 157.9 (C), 136.3 (C), 127.3 (2 x CH), 114.3 (2 x CH), 72.3 (C), 55.4 (CH_3), 47.1 (CH_2), 44.9 (CH), 33.1 (CH_2), 31.7 (CH_2), 9.8 (CH_3), 8.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1591.

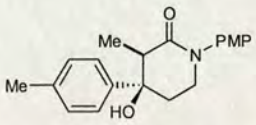


(±)-(3*R*,4*R*)-4-Hydroxy-4-*iso*-butyl-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (90c). The title compound was prepared according to general procedure E from **89c** (289 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a white solid (186 mg, 64%). m.p. 120-121 °C; IR ($CHCl_3$) 3417 (OH), 2952, 1632 (C=O), 1606, 1511, 1334, 1298, 1245, 1034, 829 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.15 (2H, d, J = 8.6 Hz, Ar**H**), 6.90 (2H, d, J = 8.6 Hz, Ar**H**), 3.87 (1H, ddd, J = 12.0, 9.9, 5.1 Hz, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.46 (1H, ddd, J = 12.0, 5.7, 4.4 Hz, C**H**$_2$N), 2.52 (1H, q, J= 7.2 Hz, C**H**C=O), 2.13-2.07 (1H, m, C**H**$_2$CH$_2$N), 2.04-1.96 (1H, m, C**H**$_2$CH$_2$N), 1.89-1.79 (1H, m, (CH$_3$)$_2$C**H**), 1.60-1.49 (2H, m, (CH$_3$)$_2$CHC**H**$_2$), 1.31 (3H, d, J = 7.2 Hz, C**H**$_3$CHC=O), 1.04 (3H, d, J = 6.6 Hz, (C**H**$_3$)$_2$CH), 1.00 (3H, d, J = 6.6 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.2 (C), 158.0 (C), 136.3 (C), 127.3 (2 x CH), 114.3 (2 x CH), 72.6 (C), 55.4 (CH_3), 49.3 (CH_2), 47.1 (CH_2), 46.5 (CH), 32.4 (CH_2), 25.0 (CH_3), 24.4 (CH_3), 24.0 (CH), 10.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{26}NO_3$ $[M+H]^+$: 292.1907, found: 292.1910.

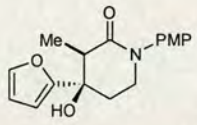


(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3,4-dimethylpiperidin-2-one (90d). The title compound was prepared according to general procedure E from **89d** (247 mg, 1.00 mmol) for a reaction time of 2.5 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (165 mg, 66%). Slow evaporation of a $CDCl_3$ solution of **90d** was found to give colourless crystals suitable for X-ray diffraction. m.p. 121-123 °C; IR ($CHCl_3$) 3410 (OH), 2942, 1631 (C=O), 1605, 1512, 1335, 1245, 1035, 830 cm^{-1};

^{1}H NMR (250 MHz, $CDCl_3$) δ 7.15 (2H, d, J = 8.9 Hz, Ar**H**), 6.90 (2H, d, J = 8.9 Hz, Ar**H**), 3.90 (1H, ddd, J = 12.1, 8.8, 6.7 Hz, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$), 3.50-3.41 (1H, m, C**H**$_2$N), 2.49 (1H, q, J = 7.2 Hz, CH_3C**H**), 2.06-2.01 (2H, m, C**H**$_2$$CH_2$N), 1.77 (1H, br s, O**H**), 1.40 (3H, s, C**H**$_3$COH), 1.34 (3H, d, J = 7.2 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 158.0 (C), 136.3 (C), 127.4 (2 x CH), 114.3 (2 x CH), 70.2 (C), 55.4 (CH_3), 47.2 (CH_2), 47.0 (CH), 35.6 (CH_2), 28.4 (CH_3), 10.1 (CH_3); HRMS (FAB) Exact mass calcd for $C_{14}H_{20}NO_3$ $[M+H]^+$: 250.1438, found: 250.1447.

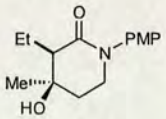


(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-(4-methylphenyl)piperidin-2-one (90e). The title compound was prepared according to general procedure E from **89e** (323 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (207 mg, 64%). m.p. 173-174 °C; IR ($CHCl_3$) 3395 (OH), 2941, 1629 (C=O), 1605, 1510, 1335, 1299, 1244, 1034, 817 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.36 (2H, d, J = 8.1 Hz, Ar**H**), 7.22 (2H, d, J = 8.1 Hz, Ar**H**), 7.19 (2H, d, J = 8.9 Hz, Ar**H**), 6.92 (2H, d, J = 8.9 Hz, Ar**H**), 4.02 (1H, ddd, J = 11.7, 11.7, 4.6 Hz, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$), 3.47 (1H, ddd, J = 11.7, 5.7, 2.8 Hz, C**H**$_2$N), 3.02 (1H, q, J= 7.2 Hz, CH_3C**H**), 2.46-2.38 (1H, m, C**H**$_2$$CH_2$N), 2.38 (3H, s, C**H**$_3$$C_6H_4$), 2.26 (1H, s, O**H**), 2.10 (1H, ddd, J = 13.9, 4.6, 2.8 Hz, C**H**$_2$$CH_2$N), 1.14 (3H, d, J = 7.2 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.0 (C), 158.0 (C), 142.8 (C), 136.9 (C), 136.2 (C), 129.3 (2 x CH), 127.4 (2 x CH), 124.4 (2 x CH), 114.3 (2 x CH), 74.6 (C), 55.4 (CH_3), 47.6 (CH_2), 46.4 (CH), 36.8 (CH_2), 20.9 (CH_3), 10.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1749.

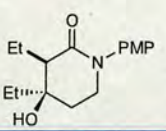


(±)-(3*R*,4*R*)-4-Furan-2-yl-4-hydroxy-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (90f). The title compound was prepared according to general procedure E from **89f** (299 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give an off-white solid (160 mg, 53%). m.p. 178-180 °C; IR ($CHCl_3$) 3375 (OH), 2938, 1631 (C=O), 1605, 1510, 1335, 1299, 1245, 1153, 1034

cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.42-7.41 (1H, m, C**H**), 7.15 (2H, d, J = 8.5 Hz, Ar**H**), 6.91 (2H, d, J = 8.5 Hz, Ar**H**), 6.39-6.38 (1H, m, C**H**), 6.34-6.33 (1H, m, C**H**), 3.93 (1H, ddd, J = 12.0, 9.8, 4.9 Hz, C**H**$_2$N), 3.81 (3H, s, OC**H**$_3$), 3.43 (1H, app dt, J = 12.0, 5.5 Hz, C**H**$_2$N), 3.06 (1H, q, J = 7.2 Hz, CH$_3$C**H**), 2.47 (1H, ddd, J = 13.8, 9.8, 5.5 Hz, C**H**$_2$CH$_2$N), 2.36 (1H, br s, O**H**), 2.25 (1H, app dt, J = 13.8, 4.9 Hz, CH$_2$C**H**$_2$N), 1.28 (3H, d, J = 7.2 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.5 (C), 158.0 (C), 157.5 (C), 142.0 (CH), 136.0 (C), 127.3 (2 x CH), 114.3 (2 x CH), 110.3 (CH), 105.4 (CH), 71.9 (C), 55.4 (CH_3), 47.0 (CH_2), 45.1 (CH), 33.8 (CH_2), 10.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{20}NO_4$ $[M+H]^+$: 302.1387, found: 302.1391.

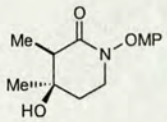


(±)-(3*R*,4*R*)-4-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-3-methylpiperidin-2-one (90g). The title compound was prepared according to general procedure F from **89g** (52 mg, 0.20 mmol) for a reaction time of 22 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (29 mg, 55%). Slow diffusion of petrol into a dichloromethane solution of **90g** was found to give colourless crystals suitable for X-ray diffraction. m.p. 109-111 °C; IR ($CHCl_3$) 3412 (OH), 2963, 1633 (C=O), 1605, 1512, 1296, 1246, 1155, 1033, 832 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.14 (2H, d, J = 8.9 Hz, Ar**H**), 6.90 (2H, d, J = 8.9 Hz, Ar**H**), 3.82-3.75 (1H, m, C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.47 (1H, ddd, J = 12.2, 6.1, 6.1 Hz, C**H**$_2$N), 2.25 (1H, dd, J = 7.2, 4.1 Hz, CH$_2$C**H**), 2.10-2.02 (1H, m, C**H**$_2$CH$_2$N), 1.97-1.76 (4H, m, CH$_3$C**H**$_2$, C**H**$_2$CH$_2$N and O**H**), 1.41 (3H, s, C**H**$_3$COH), 1.17 (3H, t, J = 7.4 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.1 (C), 158.0 (C), 136.1 (C), 127.4 (2 x CH), 114.4 (2 x CH), 70.9 (C), 55.4 (CH_3) 54.4 (CH), 47.4 (CH_2), 35.1 (CH_2), 28.5 (CH_3), 20.2 (CH_2), 14.6 (CH_3); HRMS (FAB) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1597.

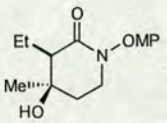


(±)-(3*R*,4*R*)-3,4-Diethyl-4-hydroxy-1-(4-methoxyphenyl) piperidin-2-one (90h). The title compound was prepared according to general procedure E from **89h** (275 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (80% EtOAc/petrol→EtOAc) to give a fluffy white solid (144 mg, 52%). m.p. 110-112 °C; IR ($CHCl_3$) 3419 (OH),

2963, 1634 (C=O), 1606, 1511, 1442, 1296, 1246, 1032, 832 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.14 (2H, d, J = 9.0 Hz, Ar**H**), 6.90 (2H, d, J = 9.0 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.78-3.71 (1H, m, C**H**$_2$N), 3.50-3.44 (1H, m, C**H**$_2$N), 2.32 (1H, dd, J = 7.7, 3.5 Hz, CH_2C**H**), 2.05-1.64 (7H, C**H**$_2$$CH_2$N, 2 x CH_3C**H**$_2$ and O**H**), 1.17 (3H, t, J = 7.4 Hz, C**H**$_3$$CH_2$), 0.99 (3H, t, J = 7.5 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.4 (C), 157.9 (C), 136.0 (C), 127.3 (2 x CH), 114.3 (2 x CH), 73.0 (C), 55.4 (CH_3), 52.7 (CH), 47.3 (CH_2), 32.9 (CH_2), 31.4 (CH_2), 20.1 (CH_2), 14.4 (CH_3), 7.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1748.

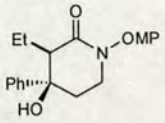


(±)-(3*R*,4*R*)-4-Hydroxy-1-(2-methoxyphenyl)-3,4-dimethyl piperidin-2-one (90i). The title compound was prepared according to general procedure E from **89i** (247 mg, 1.00 mmol) for a reaction time of 4 h and purified by column chromatography (80% EtOAc/petrol→EtOAc) to give an off-white solid (175 mg, 70%). m.p. 139-140 °C; IR ($CHCl_3$) 3418 (OH), 2973, 1633 (C=O), 1595, 1503, 1462, 1437, 1334, 1265, 1025 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31-7.26 (1H, m, Ar**H**), 7.16 (1H, dd, J = 7.6, 1.7 Hz, Ar**H**), 7.00-6.95 (2H, m, Ar**H**), 3.82 (3H, s, OC**H**$_3$), 3.71-3.62 (1H, m, C**H**$_2$N), 3.52-3.43 (1H, m, C**H**$_2$N), 2.51 (1H, q, J = 7.2 Hz, CH_3C**H**), 2.12-2.05 (3H, m, C**H**$_2$$CH_2$N and O**H**), 1.38 (3H, s, C**H**$_3$COH), 1.33 (3H, d, J = 7.2 Hz, C**H**$_3$CH); ^{13}C NMR (90.6 MHz, $C_2D_2Cl_4$, 353 K) δ 172.0 (C), 155.1 (C), 132.5 (C), 129.4 (CH), 128.8 (CH), 121.4 (CH), 112.9 (CH), 70.6 (C), 56.2 (CH_3), 47.6 (CH), 46.4 (CH_2), 35.8 (CH_2), 28.0 (CH_3), 10.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{20}NO_3$ $[M+H]^+$: 250.1438, found: 250.1440.

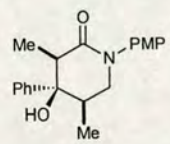


(±)-(3R,4R)-3-Ethyl-4-hydroxy-1-(2-methoxyphenyl)-4-methylpiperidin-2-one (90j). The title compound was prepared according to general procedure E from **89j** (261 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (80% EtOAc/petrol) to give a white solid (185 mg, 70%). m.p. 144-146 °C; IR ($CHCl_3$) 3408 (OH), 2964, 1636 (C=O), 1596, 1502, 1460, 1436, 1315, 1266, 1026 cm-^{1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31-7.26 (1H, m, Ar**H**), 7.15-7.13 (1H, m, Ar**H**), 7.00-6.95 (2H, m, Ar**H**),

3.82 (3H, s, OC**H**$_3$), 3.62-3.44 (2H, br m, C**H**$_2$N), 2.28 (1H, t, J = 5.8 Hz, CH$_2$C**H**), 2.20-2.06 (2H, m, CH$_2$CH$_2$N), 1.97-1.70 (3H, m, CH$_3$C**H**$_2$ and O**H**), 1.42 (3H, s, C**H**$_3$COH), 1.15 (3H, t, J = 7.4 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (90.6 MHz, $C_2D_2Cl_4$, 353 K) δ 171.8 (C), 155.2 (C), 132.4 (C), 129.4 (CH), 128.8 (CH), 121.4 (CH), 112.9 (CH), 71.4 (C), 56.2 (CH$_3$), 55.1 (CH), 46.5 (CH$_2$), 35.5 (CH$_2$), 28.3 (CH$_3$), 20.4 (CH$_2$), 14.4 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1594, found: 264.1592.

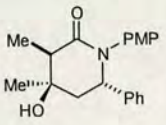


(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-1-(2-methoxyphenyl)-4-phenylpiperidin-2-one (90k). The title compound was prepared according to general procedure E from **89k** (323 mg, 1.00 mmol) but using (EtO)$_2$MeSiH (330 μL, 2.00 mmol) in place of TMDS for a reaction time of 23 h and purified by column chromatography (30% EtOAc/$CHCl_3$) to give an off-white solid (212 mg, 65%). m.p. 180-182 °C; IR ($CHCl_3$) 3388 (OH), 2931, 1631 (C=O), 1595, 1502, 1436, 1332, 1266, 1027, 752 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.54 (2H, d, J = 7.5 Hz, Ar**H**) 7.44-7.40 (2H, m, Ar**H**), 7.34-7.30 (2H, m, Ar**H**), 7.22 (1H, d, J = 7.1 Hz, Ar**H**), 7.03-6.98 (2H, m, Ar**H**), 3.87 (3H, s, OC**H**$_3$), 3.82-3.75 (1H, m, C**H**$_2$N), 3.53-3.50 (1H, m, C**H**$_2$N), 2.85-2.84 (1H, m, CH$_2$C**H**), 2.48-2.40 (2H, br m, C**H**$_2$CH$_2$N and O**H**), 2.18-2.12 (1H, m, C**H**$_2$CH$_2$N), 1.89-1.77 (1H, m, CH$_3$C**H**$_2$), 1.49-1.44 (1H, m, CH$_3$C**H**$_2$), 1.00 (3H, t, J = 7.3 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.1 (C), 154.4 (C), 145.8 (C), 131.6 (C), 128.9 (CH), 128.7 (CH), 128.3 (2 x CH), 126.9 (CH), 124.7 (2 x CH), 121.1 (CH), 112.0 (CH), 75.4 (C), 55.7 (CH$_3$), 53.2 (CH), 46.4 (CH$_2$), 37.1 (CH$_2$), 19.8 (CH$_2$), 14.5 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1753.

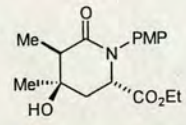


(±)-(3*R*,4*R*,5*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3,5-dimethyl-4-phenylpiperidin-2-one (98a). The title compound was prepared according to general procedure F from **97a** (65 mg, 0.20 mmol) for a reaction time of 16 h and purified by column chromatography (50% EtOAc/petrol) to give a fluffy off-white solid (51 mg, 78%). Slow evaporation of a methanol/hexane solution of **98a** was found to give colourless crystals suitable for X-ray diffraction. m.p. 204-206 °C; IR ($CHCl_3$) 3452 (OH), 1626 (C=O), 1511, 1342, 1250, 1030, 980,

913, 839, 752 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44-7.37 (4H, m, Ar**H**), 7.32-7.27 (1H, m, Ar**H**), 7.23 (2H, d, J = 8.8 Hz, Ar**H**), 6.93 (2H, d, J = 8.8 Hz, Ar**H**), 3.82 (3H, s, O**CH**$_3$), 3.78 (1H, t, J = 11.8 Hz, **CH**$_2$N), 3.48 (1H, dd, J = 11.8, 5.5 Hz, **CH**$_2$N), 3.00 (1H, q, J = 7.2 Hz, **CH**C=O), 2.65-2.55 (1H, m, **CH**CH$_2$N), 2.07 (1H, br s, O**H**), 1.04 (3H, d, J = 7.2 Hz, **CH**$_3$CHC=O), 0.66 (3H, d, J = 6.7 Hz, **CH**$_3$CHCH$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.6 (C), 158.0 (C), 143.9 (C), 136.1 (C), 128.5 (2 x CH), 127.4 (2 x CH), 126.9 (CH), 124.8 (2 x CH), 114.4 (2 x CH), 77.1 (C), 55.4 (CH_3), 54.6 (CH_2), 47.5 (CH), 38.4 (CH), 12.4 (CH_3), 9.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1747.

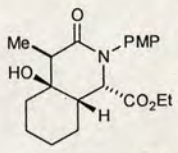


(3*R*,4*R*,6*S*)-4-Hydroxy-1-(4-methoxyphenyl)-3,4-dimethyl-6-phenylpiperidin-2-one (98b). The title compound was prepared according to general procedure F from **97b** (65 mg, 0.20 mmol) for a reaction time of 2 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a fluffy off-white solid (38 mg, 58%). m.p. 84-86 °C; $[\alpha]_D^{22}$ –81.5 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3410 (OH), 2944, 1633 (C=O), 1606, 1510, 1331, 1295, 1248, 1041, 910 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.23-7.12 (5H, m, Ar**H**), 6.92 (2H, d, J = 9.0 Hz, Ar**H**), 6.68 (2H, d, J = 9.0 Hz, Ar**H**), 5.08 (1H, dd, J = 11.3, 5.3 Hz, **CH**Ph), 3.67 (3H, s, O**CH**$_3$), 2.68 (1H, q, J = 7.1 Hz, CH$_3$C**H**), 2.31 (1H, dd, J = 14.1, 11.3 Hz, **CH**$_2$CHPh), 2.25 (1H, dd, J = 14.1, 5.3 Hz, **CH**$_2$CHPh), 1.79 (1H, br s, O**H**), 1.38 (3H, s, **CH**$_3$COH), 1.36 (3H, d, J = 7.1 Hz, **CH**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.0 (C), 157.5 (C), 141.5 (C), 134.6 (C), 128.9 (2 x CH), 128.4 (2 x CH), 127.4 (3 x CH), 113.8 (2 x CH), 70.3 (C), 61.5 (CH), 55.2 (CH_3), 46.6 (CH), 28.3 (CH_3), 9.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+H]^+$: 326.1751, found: 326.1752.



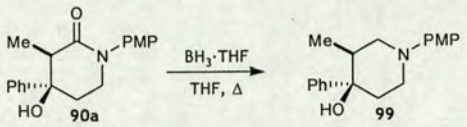
Ethyl (2*S*,4*R*,5*R*)-4-hydroxy-1-(4-methoxyphenyl)-4,5-dimethyl-6-oxopiperidine-2-carboxylate (98c). The title compound was prepared according to general procedure F from **97c** (64 mg, 0.20 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (44 mg, 68%). Slow diffusion of pentane into a dichloromethane solution of **98c** was found to give colourless crystals suitable for X-

ray diffraction. m.p. 170-172 °C; $[\alpha]_D^{22}$ –44.4 (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3247 (OH), 2930, 1746 (C=O), 1640 (C=O), 1607, 1511, 1295, 1246, 1186, 1032 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.87 (2H, d, *J* = 9.0 Hz, Ar**H**), 4.72 (1H, dd, *J* = 10.3, 5.9 Hz, C**H**CO_2Et), 4.05-3.99 (2H, m, $CO_2C\mathbf{H}_2CH_3$), 3.79 (3H, s, $OC\mathbf{H}_3$), 2.55 (1H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}$), 2.33 (1H, dd, *J* =13.7, 5.9 Hz, $C\mathbf{H}_2CHCO_2Et$), 2.14 (1H, dd, *J* = 13.7, 10.3 Hz, $C\mathbf{H}_2CHCO_2Et$), 1.79 (1H, br s, O**H**), 1.39 (3H, s, $C\mathbf{H}_3COH$), 1.29 (3H, d, *J* = 7.1 Hz, $C\mathbf{H}_3CH$), 1.10 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 171.6 (C), 158.3 (C), 134.3 (C), 128.6 (2 x CH), 114.1 (2 x CH), 70.4 (C), 61.3 (CH_2), 60.2 (CH), 55.4 (CH_3), 46.4 (CH), 39.8 (CH_2), 28.3 (CH_3), 13.9 (CH_3), 9.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{24}NO_5$ $[M+H]^+$: 322.1649, found: 322.1652.



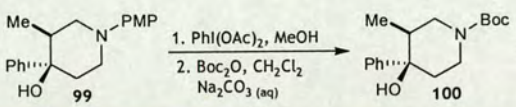
(1*S*,2*S*,5*R*,6*R*)-2-Carbethoxy-6-hydroxy-3-(4-methoxy phenyl)-5-methyl-3-azabicyclo[4.4.0]decan-4-one (98d). The title compound was prepared according to general procedure F from **97d** (72 mg, 0.20 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→40% EtOAc/petrol) to give an off-white solid (48 mg, 66%). Slow diffusion of petrol into a dichloromethane solution of **98d**wa s found to give colourless crystals suitable for X-ray diffraction. m.p. 141-143 °C; $[\alpha]_D^{22}$ +2.5 (0.80, CH_2Cl_2); IR ($CHCl_3$) 3425 (OH), 2939, 1750 (C=O), 1642 (C=O), 1607, 1510, 1294, 1245, 1187, 1029 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.15 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.85 (2H, d, *J* = 8.9 Hz, Ar**H**), 5.14 (1H, d, *J* = 5.7 Hz, C**H**CO_2Et), 4.03-3.94 (2H, m, $CO_2C\mathbf{H}_2CH_3$), 3.77 (3H, s, $OC\mathbf{H}_3$), 2.94 (1H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H}$), 2.24-2.17 (1H, m, C**H**$CHCO_2Et$), 2.05-1.99 (2H, m, $(C\mathbf{H}_2)_4$ and O**H**), 1.86-1.84 (1H, m, $(C\mathbf{H}_2)_4$), 1.73-1.61 (3H, m, $(C\mathbf{H}_2)_4$), 1.55-1.51 (1H, m, $(C\mathbf{H}_2)_4$), 1.41-1.29 (2H, m, $(C\mathbf{H}_2)_4$), 1.22 (3H, d, *J* = 7.1 Hz, $C\mathbf{H}_3CH$), 1.09 (3H, t, *J* = 7.1 Hz, $CO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.7 (C), 170.1 (C), 157.9 (C), 135.0 (C), 128.5 (2 x CH), 113.8 (2 x CH), 73.1 (C), 63.0 (CH), 60.8 (CH_2), 55.3 (CH_3), 44.0 (CH), 37.8 (CH), 37.5 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 22.9 (CH_2), 14.0 (CH_3), 8.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$: 362.1962, found: 392.1966.

(±)-(3*S*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpiperidine (99)



BH_3·THF (1 M in THF, 1.6 mL, 1.6 mmol) was added to the piperidinone **90a** (125 mg, 0.4 mmol) and the resulting solution was heated at reflux for 4 h. The reaction was cooled to room temperature and quenched with H_2O (1 mL) followed by 1 M NaOH (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (25% EtOAc/petrol) gave the *piperidine* **92** (102 mg, 86%) as an off-white solid. m.p. 114-115 °C; IR ($CHCl_3$) 3501 (OH), 2959, 1511, 1464, 1388, 1284, 1245, 1200, 1036, 825 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52-7.49 (2H, m, Ar**H**), 7.41-7.36 (2H, m, Ar**H**), 7.30-7.25 (1H, m, Ar**H**), 7.01 (2H, d, J = 9.0 Hz, Ar**H**), 6.88 (2H, d, J = 9.0 Hz, Ar**H**), 3.80 (3H, s, O**CH**$_3$), 3.46-3.40 (1H, m, C**H**$_2$N), 3.35 (1H, ddd, J = 11.8, 4.2, 1.7 Hz, C**H**$_2$N), 2.85 (1H, app t, J = 11.6 Hz, C**H**$_2$N), 2.49-2.39 (1H, m, CH_3C**H**), 2.31 (1H, ddd, J = 13.4, 13.4, 4.7 Hz, C**H**$_2$$CH_2$N), 1.82 (1H, app dt, J = 14.0, 2.5 Hz, C**H**$_2$$CH_2$N), 1.70 (1H, br s, O**H**), 0.71 (3H, d, J = 6.9 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 154.7 (C), 147.0 (C), 145.9 (C), 128.2 (2 x CH), 126.6 (CH), 124.7 (2 x CH), 118.7 (2 x CH), 114.4 (2 x CH), 73.8 (C), 55.5 (CH_3), 54.3 (CH_2), 47.2 (CH_2), 40.5 (CH_2), 39.1 (CH), 12.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{24}NO_2$ $[M+H]^+$: 298.1802, found: 298.1806.

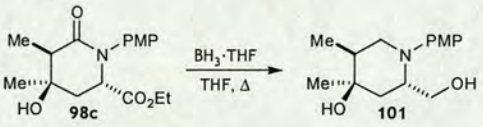
(±)-(3*S*,4*R*)-4-Hydroxy-1-(*tert*-butoxycarbonyl)-3-methyl-4-phenylpiperidine (100)



To a stirred solution of $PhI(OAc)_2$ (131 mg, 0.40 mmol) in MeOH (1.5 mL) was added a solution of the piperidine **99** (30 mg, 0.10 mmol) in MeOH (1.5 mL)

dropwise over 2 min. The solution immediately became dark red. After 30 min, 1 M HCl (1 mL) was added and the mixture was stirred for 1.5 h. The mixture was washed with CH_2Cl_2 (3 x 1 mL) and the combined organic layers were back-extracted with 1 M HCl (1 mL). To the combined aqueous layers were added CH_2Cl_2 (3 mL) followed by Boc_2O (89 mg, 0.40 mmol). The aqueous layer was made basic (pH ~ 10) by the addition of saturated aqueous Na_2CO_3 and the mixture was left to stir for 16 h. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the *carbamate* **100** (14.4 mg, 49%) as a beige solid. m.p. 152-154 °C; IR (film) 3453 (OH), 2976, 1669 (C=O), 1429, 1366, 1251, 1168, 1004, 816, 701 cm^{-1}; ^1H NMR (360 MHz, $C_2D_2Cl_4$, 353K) δ 7.40-7.38 (2H, m ArH), 7.35-7.30 (2H, m, ArH), 7.24-7.20 (1H, m, ArH), 4.01-3.96 (1H, m, CH_2N), 3.92 (1H, dd, J = 13.8, 3.8 Hz, CH_2N), 3.15 (1H, ddd, J = 13.0, 13.0, 2.9 Hz, CH_2N), 2.84 (1H, app t, J 12.4 Hz, CH_2N), 2.13-2.03 (1H, m, CH_3CH), 1.96 (1H, ddd, J = 13.5, 13.5, 5.0 Hz, CH_2CH_2N), 1.64 (1H, app dt, J = 14.0, 2.5 Hz, CH_2CH_2N), 1.60 (1H, br s, OH), 1.47 (9H, s, $C(CH_3)_3$), 0.62 (3H, d, J = 6.8 Hz, CH_3CH); ^{13}C NMR (90.6 MHz, $C_2D_2Cl_4$, 353K) δ 155.0 (C), 147.1 (C), 128.5 (2 x CH), 127.0 (CH), 79.6 (C), 74.5 (C), 46.7 (CH_2), 40.6 (CH_2), 40.4 (CH_2), 39.3 (CH), 28.8 (3 x CH_3), 12.0 (CH_3); HRMS (FAB) Exact mass calcd for $[M+H]^+$: 292.1908, found: 292.1907.

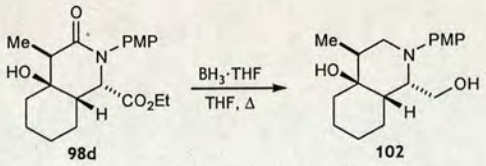
(2*S*,4*R*,5*S*)-4-Hydroxy-2-hydroxymethyl-1-(4-methoxyphenyl)-4,5-dimethylpiperidine (101)



BH_3·THF (1 M in THF, 1.84 mL, 1.84 mmol) was added to the piperidinone **98c** (74 mg, 0.23 mmol) and the resulting solution was heated at reflux for 48 h. The reaction was cooled to room temperature and quenched with H_2O (1 mL) followed by 1 M NaOH (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the

residue by column chromatography (80% EtOAc/petrol) gave the *piperidine* **101** (46 mg, 75%) as an off-white solid. m.p. 115-116 °C; $[\alpha]_D^{22}$ +11.4 (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) 3391 (OH), 2963, 2834, 1508, 1462, 1291, 1245, 1208, 1037, 835 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (2H, d, *J* = 8.9 Hz, ArH), 6.86 (2H, d, *J* = 8.9 Hz, ArH), 3.79 (3H, s, OCH_3), 3.47 (1H, dd, *J* = 11.3, 3.8 Hz), 3.27-3.22 (2H, m), 2.80 (1H, app q, *J* = 11.5 Hz), 2.73 (1H, dd, *J* = 11.5, 4.4 Hz), 2.05 (1H, br s, OH), 1.96-1.89 (1H, m, CH_2CHN), 1.85-1.73 (2H, m, CH_2CHN and CH_3CH), 1.40 (1H, br s, OH), 1.28 (3H, s, CH_3COH), 0.86 (3H, d, *J* = 6.8 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.1 (C), 144.0 (C), 126.3 (2 x CH), 114.4 (2 x CH), 69.8 (C), 63.2 (CH_2), 59.8 (CH_2), 56.5 (CH), 55.4 (CH_3), 42.4 (CH_2), 39.6 (CH), 28.3 (CH_3), 11.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{24}NO_3$ $[M+H]^+$: 266.1751, found: 266.1754.

(1*S*,2*S*,5*S*,6*S*)-2-Hydroxymethyl-3-(4-methoxyphenyl)-5-methyl-3-azabicyclo[4.4.0]decane (102)

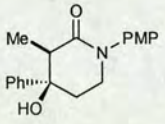


BH_3·THF (1 M in THF, 1.84 mL, 1.84 mmol) was added to the piperidine **98d** (72 mg, 0.20 mmol) and the resulting solution was heated at reflux for 36 h. The reaction was cooled to room temperature and quenched with H_2O (1 mL) followed by 1 M NaOH (3 mL). The mixture was extracted with EtOAc (3 x 5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (80% EtOAc/petrol) gave the *piperidine* **102** (39 mg, 64%) as an off white solid. m.p. 48-50 °C; $[\alpha]_D^{22}$ –84.8 (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3366 (OH), 2936, 1507, 1450, 1243, 1039, 836, 761 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.17 (2H, br d, ArH), 6.85 (2H, d, *J* = 9.0 Hz, ArH), 3.78 (3H, s, OCH_3), 3.49-3.73 (3H, m), 2.99 (1H, app t, *J* = 11.3 Hz), 2.68 (1H, br d), 2.38 (1H, br s, OH), 2.07 (2.04 (1H, m), 1.90-1.79 (2H, m), 1.69-1.61 (3H, m), 1.46-1.20 (5H,

m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 157.2 (C), 144.6 (C), 126.9 (2 x CH), 114.4 (2 x CH), 71.9 (C), 63.8 (CH_2), 60.7 (CH), 59.3 (CH_2), 55.4 (CH_3), 47.6 (CH), 37.5 (CH_2), 30.9 (CH), 25.8 (CH_2), 22.9 (CH_2), 22.7 (CH_2), 10.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{28}NO_3$ $[M+H]^+$: 306.2064, found: 306.2066.

General Procedure G: Enantioselective Cyclisations

A solution of $Cu(OAc)_2 \cdot H_2O$ (2.0 mg, 0.01 mmol) and the chiral ligand (0.01 mmol) in THF (1 mL) was stirred for 15 min before TMDS (35 μL, 0.20 mmol) was added. The solution was stirred for 5 min, after which a solution of the substrate (0.20 mmol) in THF (0.5 + 0.5 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (0.5 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (10 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclised product.



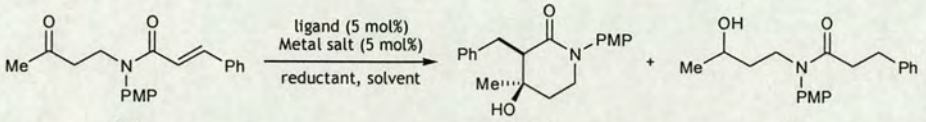
(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpiperidin-2-one (90a). The title compound was prepared according to general procedure G using **89a** (62 mg, 0.20 mmol) and *(S)*-DM-SEGPHOS **(105)** (9.2 mg, 0.01 mmol) for a reaction time of 24 h and purified by column chromatography (80% EtOAc/petrol) to give the enantioenriched product **90a** as a white solid (41 mg, 65%). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 30.9 min, t_r (major) = 43.2 min; 65% ee.

4. Cobalt-Catalysed Reductive Aldol Cyclisations

The copper-mediated cyclisation of α,β-unsaturated carbonyl components tethered to a variety of ketones through an amide linkage allows the efficient synthesis of 4-hydroxypiperidine-2-ones in moderate yields. Although the products were obtained with generally high levels of diastereoselectivity the process suffered from a number of limitations. Firstly, due to competing side reactions such as ketone reduction product yield was limited to a modest 60-70% in the best cases.[72] Secondly, the reduced electrophilicity of α,β-unsaturated amides compared with the corresponding esters[27] meant that productive cyclisations were restricted to those amide substrates were R^2 = H or Me (Table 3.3). In order to overcome the limitations of the previously described copper-mediated methodology, a search for improved reaction conditions was initiated. To this end, a number of alternative reductants and metal salts were investigated for reaction efficacy. Following the identification of an active catalyst system, a variety of 4-hydroxypiperidine-2-ones and pyrrolidin-2-ones were to be synthesised in order to gauge the robustness of the newly developed methodology.

4.1. Results and Discussion[85]

Initially, the cyclisation of cinnamic amide substrate (**89l**) was investigated (Table 4.1).



89l **90l** **91**

Entry	Reagents	Solvent	T(°C)	%Conversion[a]	90l/91
1	$Cu(OAc)_2 \cdot H_2O$, DPPF, TMDS (1 equiv)	THF	rt	77	34:66
2	$Cu(OAc)_2 \cdot H_2O$, *rac*-BINAP, TMDS (1 equiv)	THF	rt	87	39:61
3	$Cu(OAc)_2 \cdot H_2O$, DPPF, $PhSiH_3$ (1 equiv)	THF	rt	<5	-
4	$Co(dpm)_2$, $PhSiH_3$ (1 equiv)	CH_2Cl_2	rt	-[b]	-[b]
5	$Co(dpm)_2$, $PhSiH_3$ (1 equiv)	DCE	rt to 50	-[b]	-[b]
6	$Co(acac)_2 \cdot 2H_2O$, Et_3B (2 equiv)	THF/ hexane	0 to rt	<5	-
7	$Co(acac)_2 \cdot 2H_2O$, Et_2Zn (2 equiv)	THF/ hexane	0 to rt	>95	>95:5
8	$CoCl_2$, $PhCy_2P$, Et_2Zn (2 equiv)	THF/ hexane	0 to rt	>95	>95:5

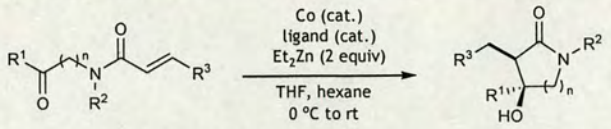
[a]Determined by ^1H NMR analysis of the unpurified reaction mixtures; [b]A complex mixture containing unidentified side-products was obtained

Table 4.1

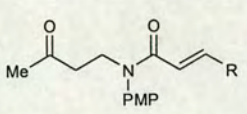
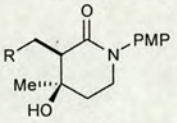
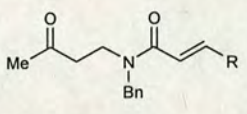
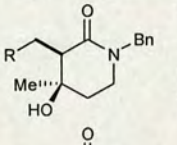
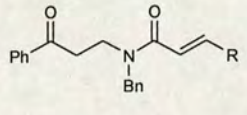
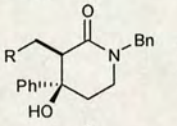
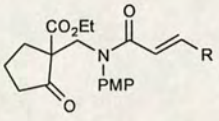
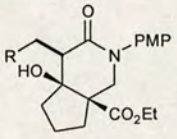
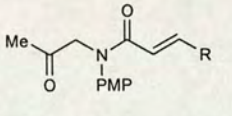
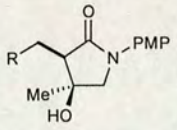
As described previously (Chapter 3), the application of the copper conditions proved ineffective giving mostly uncyclised doubly reduced starting material **91** (entry 1). The formation of **91** can be attributed to a slow rate of aldol cyclisation, allowing competitive conjugate reduction to become more prevalent. Replacement of DPPF **(25)**w ith *rac*-BINAP led to a similar result (entry 2), whereas the use of alternative silanes such as $PhSiH_3$ in place of TMDS resulted in negligible reactivity (entry 3). Consequently, alternative metal salts were considered as potential replacements for the copper-based catalyst system previously employed. In this regard, the use of an appropriate chiral ligand in conjunction with $CoCl_2$ and sodium borohydride ($NaBH_4$) has proven useful for the asymmetric conjugate reduction of α,β-unsaturated amides.[86] Predictably, conditions employing $NaBH_4$ led to rapid ketone reduction of **89l**, even at reduced temperatures. Likewise, conditions utilising a combination of cobalt dipivoloylmethane ($Co(dpm)_2$) and $PhSiH_3$, which were developed for intermolecular reductive aldol reactions by Mukaiyama[33] and subsequently extended to reductive aldol cyclisations by Krische[34] also proved

ineffective, giving complex reaction mixtures (entries 4 and 5). Recently however, organometallic reagents with β-hydrogen-containing alkyl substituents have been utilised as the stoichiometric reductant in a number of transition metal catalysed reductive couplings and cyclisations. Therefore, we explored the effectiveness of triethylborane (Et_3B) and diethylzinc (Et_2Zn) in the reaction. In the presence of 5 mol% of $Co(acac)_2 \cdot 2H_2O$, the use of Et_3B resulted in minimal reaction (entry 6), whereas the more reactive Et_2Zn led to the formation of **90l** in 89% yield with no apparent formation of the side product **91** (entry 7). In addition, it was found that the combination of 5 mol% anhydrous $CoCl_2$ and the electron rich phosphine Cy_2PPh led to augmented reaction rates giving similar levels of conversion and product distribution compared to those obtained when $Co(acac)_2$ is used as the catalyst (entry 8).

Following the development of effective conditions, the scope of the process was next investigated (Table 4.2).



Method A: $Co(acac)_2$ (5 mol%)
Method B: $CoCl_2$ (5 mol%),C y_2PPh (5.5 mol%)

Entry	Substrate		Method	Product		dr[a]	%Yield
1		R = Ph **89l**	A		**90l**	12:1	89
2		R = 2-furyl **131a**	A		**132a**	>19:1	90
3		R = ^{i}Pr **131b**	A		**132b**	>19:1	78
4		R = H **131c**	A		**132c**	9:1	88[b]
5		R = ^{i}Pr **131d**	A		**132d**	>19:1	>99[b]
6		R = Ph **131e**	A		**132e**	>19:1	97[b]
7		R = 2-furyl **131f**	A		**132f**	>19:1	>99[b]
8		R = Me **131g**	A		**132g**	>19:1	94[b]
9		R = ^{t}Bu **131h**	A		**132h**	>19:1	94[b]
10		R = H **131i**	B		**132i**	9:1	56[c]
11		R = Me **131j**	B		**132j**	>19:1	80[c]
12		R = Ph **131k**	B		**132k**	>19:1	88[c]
13		R = H **113a**	A		**114b**	9:1	47
14		R = Ph **113c**	A		**114c**	8:1	56
15		R = 2-MeOPh **131l**	B		**132l**	14:1	74
16		R = 2-furyl **131m**	A		**132m**	14:1	55
17		R = 4-ClPh **131n**	A		**132n**	5:1	41

[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures; [b]Results taken from Pekka Joensuu; [c]Results taken from Euan Fordyce

Table 4.2

Substrates containing a wide range of substitution at both the α,β-unsaturated amide and the ketone underwent cyclisation to give the corresponding 4-hydroxypiperidin-2-one products in moderate to excellent yields and with high diastereoselectivities (entries 1-12). Notably, the copper conditions previously described (Table 4.1, entry 1) proved ineffective in the majority of these cyclisations. Furthermore, the choice of nitrogen protecting greatly influenced the isolated yield of the products. Generally, the use of benzyl protection (entries 5-10) tends to result in increased yields of the cyclisation products compared to those obtained when PMP is used as the protecting group (entries 1-3).

The reaction could also be applied to the synthesis of pyrrolidin-2-ones (entries 13-17), giving the products in moderate to good yield and with generally good levels of diastereoselectivity. Most notably, in the case of pyrrolidin-2-one formation the electronics of the α,β-unsaturated amide component have a crucial role to play in the yield and selectivity of the cyclisation reaction. For example, electron rich systems gave rise to the most efficient, high yielding reactions where the diastereoselectivities were particularly high (entries 7 and 8). On the other hand, electron deficient systems resulted in the least efficient, low yielding reactions where the diastereoselectivities were very poor (entry 9). The relative stereochemistry of pyrrolidin-2-one **114c** was confirmed by X-ray crystallography (Figure 4.1) and reflected those of the 4-hydroxypiperidin-2-one products previously described.[72]

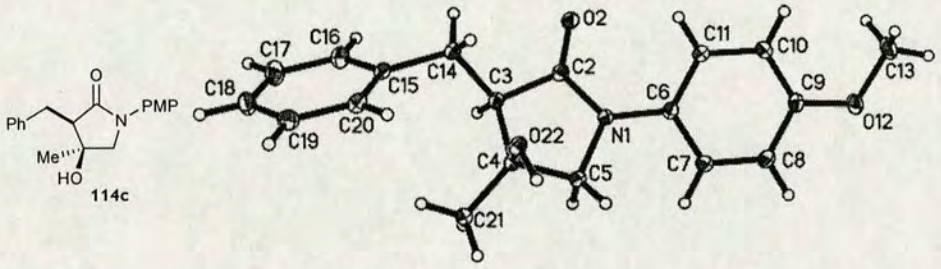
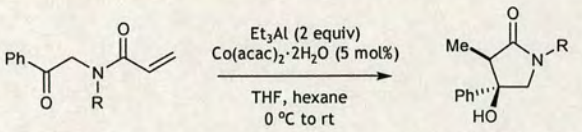


Figure 4.1

A number of complications were encountered when substrates **133a,b** containing phenyl ketones were utilised; in contrast to methyl ketones **113a,c** and **132l-n** (Table 4.2, entries 13-17), the desired pyrrolidin-2-one products were obtained in <20% yield with an assortment of other unidentified side-products. This is most likely due to the decreased electrophilicity of phenyl ketones compared to alkyl ketones. Nevertheless, replacement of Et_2Zn with Et_3Al allowed the corresponding pyrrolidin-2-ones **134a,b** to be isolated in moderate yield with good to excellent levels of diastereoselection (eqs 35 and 26).



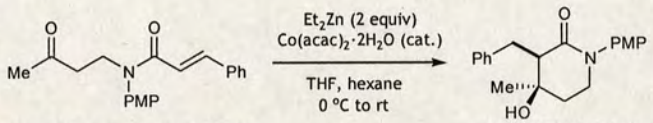
133a R = PMP → **134a** (57% yield, >19:1 dr)[a] (35)

133b R = PMB → **134b** (53% yield, 8:1 dr)[a] (36)

[a] Results taken from Oscar Prieto Congost, Post-Doctoral report 2006

However, analogues of **133a,b** containing substituted α,β-unsaturated amides did not react under any conditions examined.

Although 5 mol% of the cobalt source was used for convenience, the reaction is tolerant of far lower catalyst loadings. For example, on a 5 mmol scale, substrate **89l** underwent cyclisation using 0.5 mol% of $Co(acac)_2 \cdot 2H_2O$ to provide **90l** in 79% yield and with no loss of diastereoselection (eqs 37 and 38).

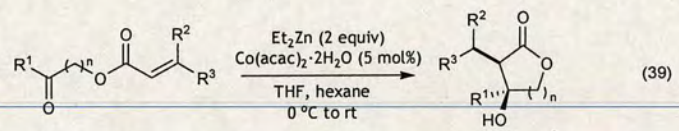


89l $Co(acac)_2 \cdot 2H_2O$ (0.5 mol%) → **90l** 79% yield, 9:1 dr (37)

89l $Co(acac)_2 \cdot 2H_2O$ (0.0 mol%) → **90l** nr (38)

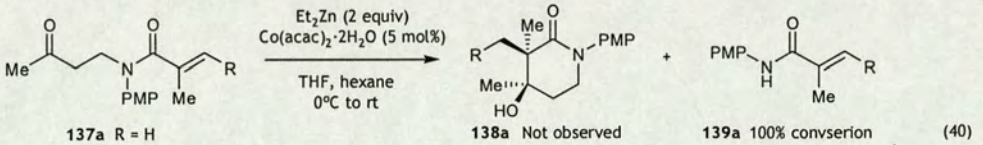
In the absence of $Co(acac)_2 \cdot 2H_2O$ the reaction failed to initiate, indicating that cobalt is essential for mediating the cyclisation reaction (eq 38).

As detailed previously (Chapter 1 and 3) our copper-catalysed methodology could be used to great effect in the reductive aldol cyclisation of a variety of ketones tethered to α,β-unsaturated components through an ester-linkage.[27] However, the application of our cobalt-mediated conditions to the synthesis of β-hydroxylactones **136** proved to be ineffective, resulting in a mixture of unidentifiable products (eq 39).



135 → **136** *Poor reactivity* (39)

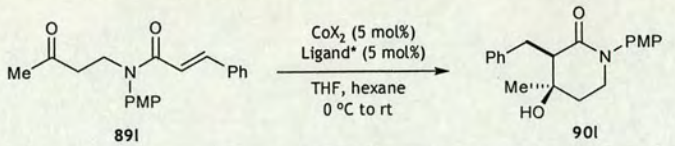
The construction of all-carbon quaternary stereogenic centres remains an important goal for organic chemists. In particular the synthesis of heterocyclic ring systems bearing vicinal quaternary centres offers a significant challenge. Hence, we envisioned that our newly developed cobalt catalysed reductive aldol methodology could be extended to the synthesis of 4-hydroxypiperidin-2-ones containing an all-carbon quaternary centre in the 3-position of the heterocyclic ring. Unfortunately, when substrates **137a,b** were exposed to our standard conditions the products of cyclisation **138a,b** were not observed. Instead, amides **139a,b** were obtained in ~80% yield resulting from conjugate elimination of the substrates (eqs 40 and 41).



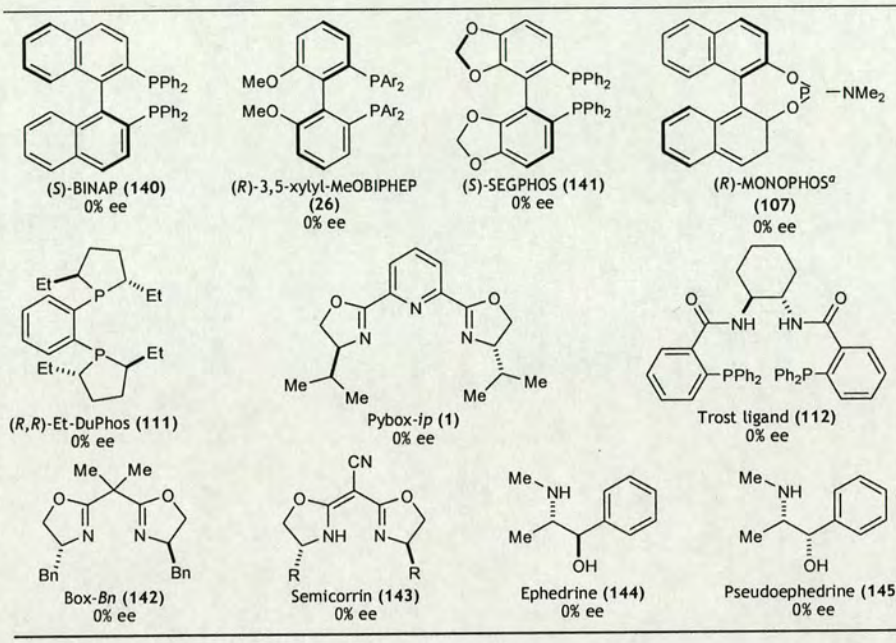
137a R = H **138a** Not observed **139a** 100% convserion (40)

137b R = Me **138b** Not observed **139b** 100% conversion (41)

Since enantioselective carbon-carbon bond forming reactions are invaluable tools in organic synthesis. A number of chiral non-racemic ligands were investigated in order to probe a possible asymmetric variant of this methodology (Table 4.3).



891 901



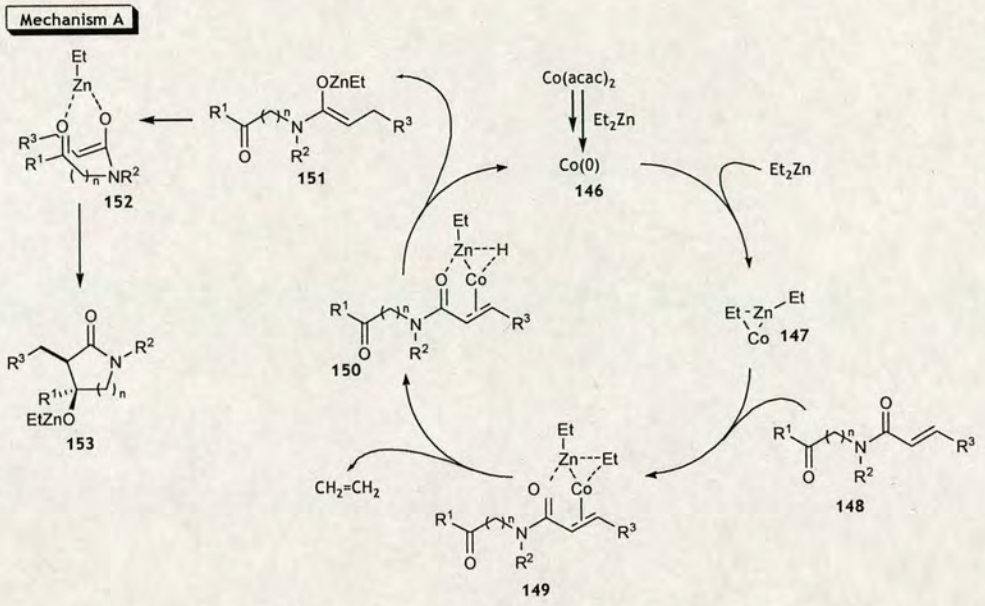
[a]10 mol% of ligand used

Table 4.3

Unfortunately, in the presence of substoichiometric quantities of a variety of chiral ligands only racemic products were obtained (Table 4.3). Alternative cobalt salts such as $CoCl_2$ and $CoBr_2(PPh_3)_2$ also gave rise to similar results.

4.1.1. Proposed Mechanism

At this stage, lacking any literature presedent, only speculative mechanisms for the cobalt-catalysed reductive aldol cyclisation can be proposed. For example, a plausible mechanism which involves the intervention of discrete enolate intermediates is detailed below (Scheme 4.1).

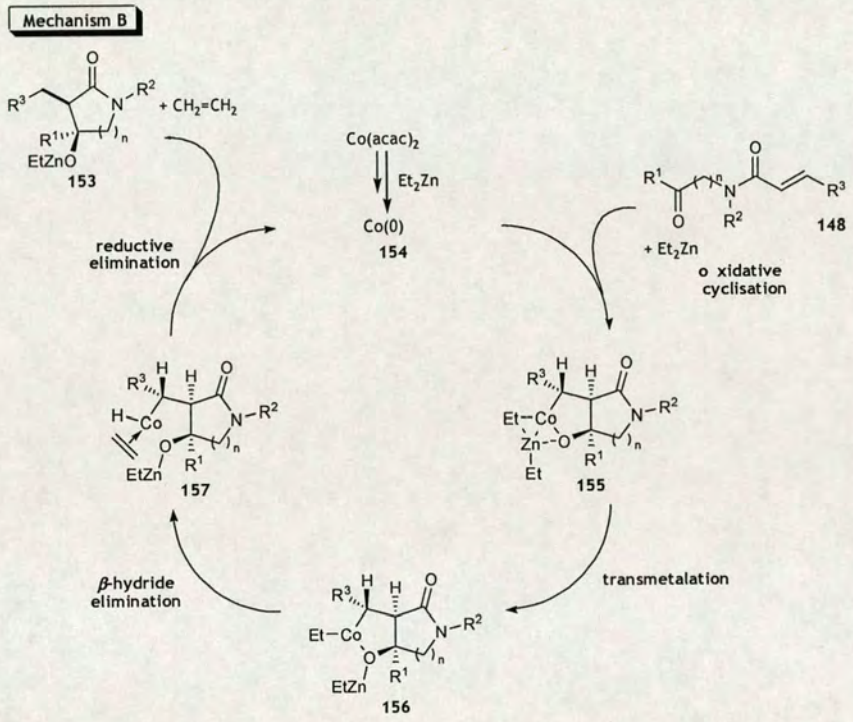


Scheme 4.1

Treatment of $Co(acac)_2 \cdot 2H_2O$ or $CoCl_2$ with Et_2Zn results in the formation of low valent cobalt species **146**, presumably through sequential transmetalation/reductive elimination. A combination of Co(0) and diethylzinc may lead to the bimetallic intermediate **147** containing a three-centre-two-electron bridging interaction. The coordination of **147** with substrate **148** would provide structure **149**, which would undergo a β-hydride elimination to produce cobalt hydride **150**. Rearrangement of **150** can then occur to give zinc enolate **151**, which would undergo a reductive aldol cyclisation to produce the zinc alkoxide **153** and regenerate Co(0). In this case the observed stereochemical outcome can be rationalised by invoking a chelated Zimmerman-Traxler-type transition state[13] **152** and preferential *Z*-enolate formation. Even though this type of bridging interaction has not been disclosed for a cobalt-catalysed reaction, it has been proposed for a number of associated Ni(0)-catalysed alkylative couplings to account for the accelerating effect of organozinc reagents.[69a,b] Moreover, it has been observed by X-ray crystallography for cobalt[69a] and nickel complexes with Grignard and organoaluminium reagents. Alternative mechanistic possibilities are comparable to those proposed for catalytic variants of the

Reformatsky reaction utilising α-bromocarbonyl compounds and dialkylzinc reagents mediated by rhodium[87a] and nickel.[87b,c]

Another mechanistic pathway initially considered, involves the Et_2Zn-assisted oxidative cyclisation of a low-valent cobalt species with substrate **142** to form the cobaltacycle **149** (Scheme 4.2).

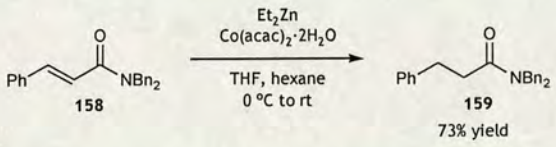


Scheme 4.2

Oxidative cyclisation of the Co(0) species **154** with the alkene and ketone of substrate **148** would result in the oxacobaltacycle **155**. Cleavage of the oxacobaltacycle **155** by transmetalation would furnish cobalt-ethyl species **156**, which following β-hydride elimination would generate cobalt-hydride species **157**. Reductive elimination of **157** would produce the product as the zinc alkoxide **153** (protonated upon work-up), ethylene and Co(0) **154**, which re-enters the catalytic cycle. The observed relative stereochemistry of the cyclised products is related to the formation of the bicyclic intermediate preferring to adopt an energetically more

favourable *cis*-ring junction as apposed to the higher energy *trans*-ring junction. The formation of metallacycles as reaction intermediates has been reported in a number of cobalt-[69] and nickel-catalysed[46,59,67] reductive couplings. Nonetheless, several observations led to the conclusion that this particular reaction pathway is not active. As illustrated previously, the addition of substoichiometric quantities of a variety of chiral ligands led only to racemic products (Table 4.3), indicating that cobalt is not involved in the stereochemical-determining step.

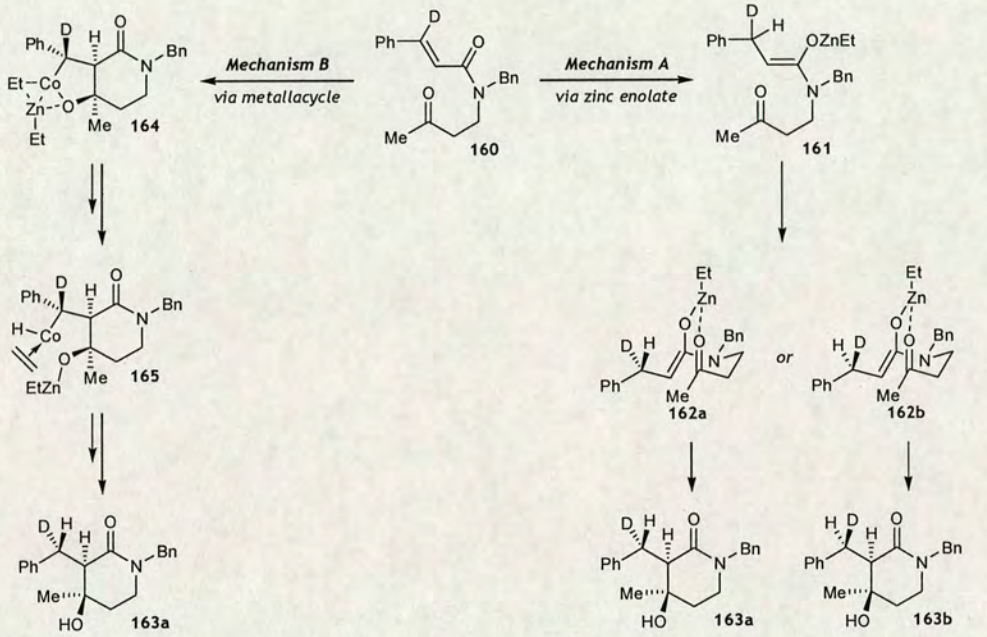
In an effort to identify which mechanism is in operation, we examined the reaction of α,β-unsaturated amide **158** in the absence of the pendant ketone π-system to our standard conditions (eq 42; results taken from Pekka Joensuu). Theoretically, mechanism A (Scheme 4.1) does not require the presence of a second electrophilic π-component until after the zinc enolate is formed, however, in mechanism B the ketone π-component is an essential prerequisite for oxidative cyclisation to form the proposed oxacobaltacycle (Scheme 4.2). Consequently, if mechanism A is in operation one would expect to observe the product of conjugate reduction. In the event, exposure of **158** to our standard conditions provided the desired reduced amide **159** in 73% yield. Although, this observation suggests that Mechanism A is likely to be operative, it is not possible to completely exclude Mechanism B at this stage.



(42)

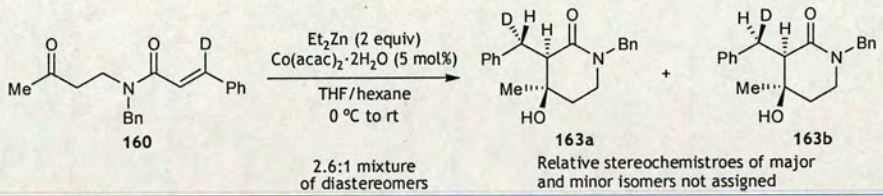
Given that the preceding experiment indicated that the reaction is proceding through mechanism A (Scheme 4.1), we next conducted the cyclisation of deuterium labelled substrate **160** (Scheme 4.3). In principle, if mechanism A is operative via the proposed zinc enolate **161**, we should theoretically expect to observe the cyclised product as a *ca.* 1:1 mixture of diastereomers **163a** and **163b**. This would be due to the diastereomeric Zimmerman-Traxler-type transition states[13] **162a** and **162b** possessing near identical energies. On the other hand, if mechanism B is operative,

the concerted nature of the oxidative cyclisation would be expected to provide metallacycle **164** with the relative stereochemistry illustrated. Subsequent reductive elimination of cobalt hydride **165** that proceeds with retention of configuration would be expected to produce a single diastereomer of cyclised product **163a**.



Scheme 4.3

In the event, the cobalt-catalysed reductive cyclisation of **160** afforded a 2.6:1 inseparable mixture of diastereomers **163a** and **163b** as determined of NMR spectroscopy of the unpurified reaction mixture (eq 43; results taken from Pekka Joensuu).



(43)

From this result several possible explanations maybe invoked to rationalise the observed diastereomeric ratio. Firstly, both mechanism A and B are operative as

competing reaction pathways. Secondly, mechanism B is operative, but one or more steps in the pathway are not stereospecific. This may in part be due to the conformational lability of a carbon–cobalt bond allowing epimerisation. Thirdly, if mechanism A is operative, initial precoordination of either cobalt or zinc with both carbonyl groups could facilitate a degree of facial selectivity during the reduction of the α,β-unsaturated system. This is probable as the chelate effect will favour the substrate acting as a bidenate ligand and the coordination of oxygen will activate the α,β-unsaturated system to reduction. Although on the available evidence, mechanism B cannot be completely discounted at this stage, we presently favour a variation of mechanism A as the probable reaction pathway based on the results from the deuterium-labelling studies.

4.2. Conclusions and Future Work

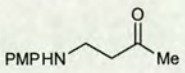
We have developed a noval synthetic methodology where a large variety of 4-hydroxypiperidin-2-ones and pyrrolidin-2-ones can be efficiently synthesised in excellent yields and diastereoselectivities. The reaction tolerates a wide variety of substrate substitution. The catalyst system is highly active with a catalyst loading of 0.5 mol% of $Co(acac)_2$ facilitating the cyclisation of **89l** in 79% yield over 4 hours. However, the combination of a variety of chiral non-racemic ligands has yet to yield any enantioselectivities, suggesting that the cobalt catalyst is not involved in the stereochemical determining step. Deuterium labelling studies have indicated that the mechanism most likely procedes through discrete enolate intermediates (Mechanism A); however, lacking further study the alternative reaction pathways cannot be discounted at this stage.

4.3. Experimental

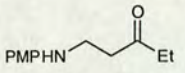
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Crotonoyl chloride was distilled from CaH_2. Commercially available $CoCl_2$ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[80] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated

mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

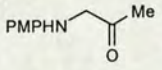
Preparation of Aminoketones



4-(4-Methoxyphenylamino)butan-2-one (118). Prepared according to a previously reported procedure (Chapter 3.3).

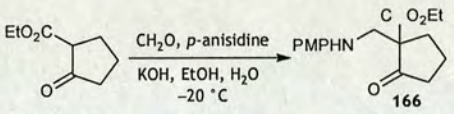


5-(4-Methoxyphenylamino)pentan-3-one (119). Prepared according to a previously reported procedure (Chapter 3.3).



1-(4-Methoxyphenyl)aminopropanone (126). Prepared according to a previously reported procedure (Chapter 3.3).

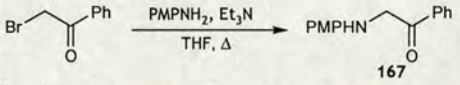
1-[(4-Methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (166)



A solution of *p*-anisidine (4.73 g, 38.4 mmol) and aqueous formaldehyde solution (37% wt in H_2O, 2.88 mL, 38.4 mmol) in EtOH (200 mL) was stirred at room temperature for 10 min. Ethyl 2-oxocyclopentanecarboxylate (4.00 g, 25.6 mmol) was added in one portion, the resulting mixture was cooled to –20 °C, and KOH (4.31 g, 76.8 mmol) was then added portionwise over 5 min. The reaction mixture was stirred at –20 °C for 30 min and then poured into saturated aqueous NH_4Cl solution (200 mL). The mixture was extracted with CH_2Cl_2 (3 x 150 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the *aminoketone* **166** (7.01 g, 94%) as a pale brown oil. IR (film) 3388 (NH), 2959, 1747 (C=O), 1719 (C=O), 1514, 1465, 1234, 1176, 1036, 822 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.76

(2H, dm, J = 9.0 Hz, Ar**H**), 6.60 (2H, d, J = 9.0 Hz, Ar**H**), 4.16 (2H, qd, J = 7.1, 1.2 Hz, OC**H**$_2$CH$_3$), 3.73 (3H, s, OC**H**$_3$), 3.48 (1H, d, J = 13.1 Hz, C**H**$_2$N), 3.42 (1H, d, J = 13.1 Hz, C**H**$_2$N), 2.56-2.41 (2H, m, C**H**$_2$CH$_2$C**H**$_2$), 2.34-1.93 (5H, m, C**H**$_2$C**H**$_2$C**H**$_2$ and N**H**), 1.23 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 214.7 (C), 170.9 (C), 152.3 (C), 142.2 (C), 114.7 (2 x CH), 114.5 (2 x CH), 61.5 (CH_2), 61.0 (C), 55.6 (CH_3), 47.7 (CH_2), 38.1 (CH_2), 32.0 (CH_2), 19.6 (CH_2), 13.9 (CH_3).

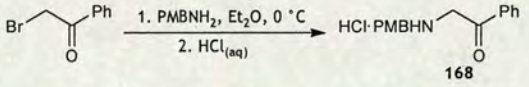
2-(4-Methoxyphenyl)aminoacetophenone (167)



167

A solution of 2-bromoacetophenone (3.98 g, 20.0 mmol), *p*-anisidine (2.23 g, 18.1 mmol) and Et_3N (5.05 mL, 36.2 mmol) in THF (100 mL) was heated at reflux for 24 h. The reaction mixture was cooled to room temperature and washed with brine (100 mL). The aqueous layer was separated and extracted with EtOAc (2 x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by recrystallization (EtOAc/petrol) to give the aminoketone **167** as a dark orange solid (1.80 g, 40%) that displayed identical spectroscopic data to those reported previously.

2-(4-Methoxybenzyl)aminoacetophenone hydrochloride (168)

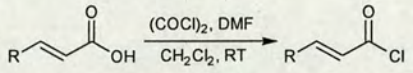


168

To a solution of *p*-methoxybenzylamine (5.20 mL, 40.0 mmol) in Et_2O (20 mL) at 0 °C was added a solution of 2-bromoacetophenone (3.90 g, 20.0 mmol) in Et_2O (20 mL) over 5 min. The mixture was stirred at 0 °C for 12 h, and the resulting white precipitate was removed by filtration. The precipitate was washed with Et_2O (2 x 20 mL), and the combined filtrate and washings were cooled to 0 °C. 38% Aqueous HCl solution (2.5 mL) was added dropwise over 1 min to give a brown precipitate, which was filtered, washed with acetone (2 x 5 mL) and recrystallized from EtOH/Et_2O to

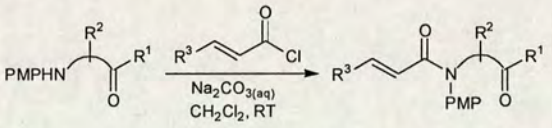
give the aminoketone hydrochloride **168** as a white solid (1.40 g, 24%) that displayed identical spectroscopic data to those reported previously.

Preparation of α,β-Unsaturated Acid Chlorides: General Procedure H



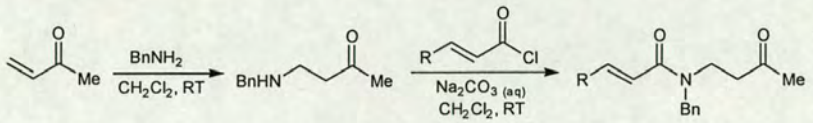
Oxalyl chloride (1.21 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.10 equiv) and DMF (0.25 equiv) in CH_2Cl_2 (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of α,β-unsaturated acid chloride which was used directly in the next step.

Preparation of Cyclization Precursors: General Procedure D



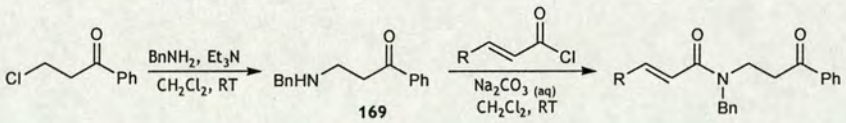
The appropriate α,β-unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure H, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate aminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of aminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of aminoketone). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization substrate.

Preparation of Cyclization Precursors: General Procedure I



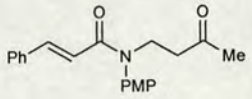
A solution of benzylamine (1.0 equiv) and methyl vinyl ketone (1.1 equiv) in CH_2Cl_2 (2.5 mL/mmol of benzylamine) was stirred at 0 °C for 18 h. Saturated aqueous Na_2CO_3 solution (2.5 mL/mmol of benzylamine) followed by the appropriate acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure H, 1.21 equiv) were then added dropwise or portionwise and the mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were washed with 10% HCl solution (x 1), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization substrate.

Preparation of Cyclization Precursors: General Procedure J

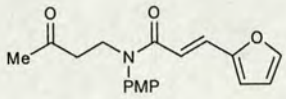


Benzylamine (1.0 equiv) was added over 1 min to a solution of 3-chloropropiophenone (1.1 equiv) and Et_3N (3.3 equiv) in THF (2.5 mL/mmol of benzylamine) at room temperature and the mixture was stirred for 18 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and EtOAc. The aqueous layer was separated and extracted with EtOAc (x 2), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting amine **169** was used directly in the next step without further purification.

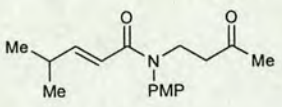
The appropriate α,β-unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure H, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the unpurified amine **169** (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of **169**) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of **169**). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization substrate.



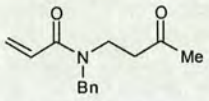
***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenoate (89l)**. Prepared according to a previously reported procedure (Chapter 3.3)



***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (131a)**. The title compound was prepared according to General Procedure D from the amine **118** (1.00 g, 5.20 mmol) and the acid chloride (prepared according to General Procedure A) derived from 3-(2-furyl)acrylic acid (1.10 g, 7.80 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow/orange solid (1.01 g, 61%). m.p. 94-95 °C; IR ($CHCl_3$) 2934, 1713 (C=O), 1664 (C=O), 1614, 1511, 1392, 1250, 1017, 840, 748 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39 (1H, d, J = 15.3 Hz, C**H**=CHC=O), 7.31 (1H, d, J = 1.6 Hz, C**H**), 7.09 (2H, d, J = 8.9 Hz, Ar**H**), 6.93 (2H, d, J = 8.9 Hz, Ar**H**), 6.47 (1H, d, J = 3.3 Hz, C**H**), 6.36 (1H, dd, J = 3.3, 1.6 Hz, C**H**), 6.14 (1H, d, J = 15.3 Hz, C**H**C=O), 4.02 (2H, t, J = 7.4 Hz, C$\mathbf{H_2}$N), 3.84 (3H, s, O$\mathbf{CH_3}$), 2.77 (2H, t, J = 7.4 Hz, C$\mathbf{H_2}$$CH_2$N), 2.13 (3H, s, C$\mathbf{H_3}$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 207.0 (C), 168.2 (C), 158.9 (C), 151.5 (C), 143.8 (CH), 134.4 (C), 129.3 (2 x CH), 128.5 (CH), 116.3 (CH), 114.8 (2 x CH), 113.7 (CH), 112.0 (CH), 55.4 (CH_3), 45.2 (CH_2), 41.5 (CH_2), 30.0 (CH_3); HRMS (ES) Mass calcd for $C_{18}H_{20}NO_4$ $[M+H]^+$: 314.1387, found: 314.1386.

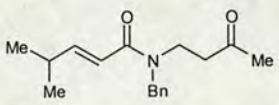


***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-4-methylpent-2-enamide (131b)**. The title compound was prepared according to General Procedure D from the amine **118** (1.00 g, 5.20 mmol) and the acid chloride (prepared according to General Procedure A) derived from 4-methyl-2-pentenoic acid (890 mg, 7.80 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow/orange solid (1.10 g, 73%). m.p. 95-96 °C; IR ($CHCl_3$) 2961, 1713 (C=O), 1661 (C=O), 1627, 1511, 1394, 1250, 1031, 838, 736 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.05 (2H, d, J = 8.9 Hz, Ar**H**), 6.90 (2H, d, J = 8.9 Hz, Ar**H**), 6.81 (1H, dd, J = 15.2, 7.0 Hz, NCH=C**H**), 5.58 (1H, d, J = 15.2 Hz, NC**H**=CH), 3.96 (2H, t, J = 7.5 Hz, C**H**$_2$N), 3.83 (3H, s, O**CH**$_3$), 2.74 (2H, t, J = 7.5 Hz, C**H**$_2$CH$_2$N), 2.27 (1H, heptet, J = 7.0 Hz, C**H**(CH$_3$)$_2$), 2.12 (3H, s, C**H**$_3$), 0.91 (6H, d, J = 7.0 Hz, CH(C**H**$_3$)$_2$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 207.1 (C), 166.5 (C), 158.8 (C), 152.4 (CH), 134.7 (C), 129.3 (2 x CH), 118.7 (CH), 114.6 (2 x CH), 55.4 (CH_3), 45.1 (CH_2), 41.6 (CH_2), 31.0 (CH), 30.0 (CH_3), 21.5 (2 x CH_3); HRMS (ES) Mass calcd for $C_{17}H_{23}NO_3$ $[M+H]^+$: 289.1673, found: 289.1674.

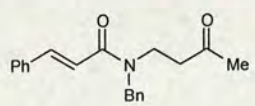


***N*-Benzyl-*N*-(3-oxobutyl)propenamide (131c)**. The title compound was prepared according to General Procedure D from methyl vinyl ketone (0.94 mL, 11.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and acryloyl chloride (1.02 mL, 12.1 mmol) for a reaction time of 3 h. The product was purified by column chromatography (50% EtOAc/petrol) to give a colorless oil (1.08 g, 47%) as a 2:1 mixture of rotamers. IR (film) 3063, 1714 (C=O), 1648 (C=C), 1613, 1471, 1447, 1371, 978, 732, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.39-7.28 (4H, m, Ar**H**), 7.20-7.18 (1H, m, Ar**H**), 6.56 (1H, dd, J = 16.7, 10.2 Hz, CH$_2$=C**H**), 6.41 (1H, dd, J = 16.7, 2.1 Hz, C**H**$_2$=CH), 5.70 (1H, dd, J = 10.2, 2.1 Hz, C**H**$_2$=CH), 4.70 (2H, s, C**H**$_2$Ph), 3.65 (2H, t, J = 6.7 Hz, CH$_2$C**H**$_2$N), 2.85 (2H, t, J = 6.7 Hz, C**H**$_2$CH$_2$N), 2.14 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.39-7.28 (4H, m, Ar**H**), 7.20-7.18 (1H, m, Ar**H**), 6.68 (1H, dd, J = 16.7, 10.3 Hz CH$_2$=C**H**), 6.48 (1H, dd, J = 16.7, 1.9 Hz, C**H**$_2$=CH), 5.79 (1H, dd, J = 10.3, 1.9 Hz, C**H**$_2$=CH), 4.68 (2H, s, C**H**$_2$Ph), 3.63 (2H, t, J = 7.0 Hz, CH$_2$C**H**$_2$N), 2.66 (2H, t, J = 7.0 Hz, C**H**$_2$CH$_2$N), 2.09 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture

of rotamers – not fully assigned) δ 206.9 (C), 205.6 (C), 166.5 (C), 165.9 (C), 137.2 (C), 136.6 (C), 128.5 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH_2), 127.6 (CH), 127.3 (CH), 127.1 (CH), 126.0 (CH), 51.8 (CH_2), 48.9 (CH_2), 42.3 (CH_2), 42.0 (CH_2), 41.5 (CH_2), 41.4 (CH_2), 29.8 (CH_3), 29.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_2$ $[M+H]^+$: 232.1332, found: 232.1332.

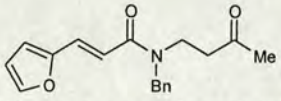


***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-4-methylpent-2-enamide (131d)**. The title compound was prepared according to General Procedure I from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from 4-methyl-2-pentenoic acid (2.76 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a white solid (2.36 g, 43%) as a 2:1 mixture of rotamers. m.p. 59-61 °C; IR ($CHCl_3$) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.35-7.23 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 6.90 (1H, dd, J = 15.1, 7.0 Hz, CHC**H**=), 6.12 (1H, dd, J = 15.1, 1.0 Hz, CHCH=C**H**), 4.64 (2H, s, C**H**$_2$Ph), 3.59 (2H, t, J = 6.8 Hz, CH_2C**H**$_2$N), 2.80 (2H, t, J = 6.8 Hz, C**H**$_2$$CH_2$N), 2.43-2.34 (1H, m, $(CH_3)_2$C**H**), 2.10 (3H, s, C**H**$_3$C=O), 0.99 (6H, J = 6.8 Hz, $(CH_3)_2$CH); (Minor rotamer) δ 7.35-7.23 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 6.97 (1H, dd, J = 15.1, 7.0 Hz, CHC**H**=), 6.21 (1H, d, J = 15.1 Hz, CHCH=C**H**), 4.64 (2H, s, C**H**$_2$Ar), 3.59 (2H, t, J = 7.1 Hz, CH_2C**H**$_2$N), 2.62 (2H, t, J = 7.1 Hz, C**H**$_2$$CH_2$N), 2.51-2.43 (1H, m, $(CH_3)_2$C**H**), 2.06 (3H, s, C**H**$_3$C=O), 1.07 (6H, d, J = 6.7 Hz, $(CH_3)_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 167.4 (C), 166.8 (C), 153.9 (CH), 153.4 (CH), 137.7 (C), 137.2 (C), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 117.3 (CH), 116.9 (CH), 52.2 (CH_2), 49.3 (CH_2), 42.8 (CH_2), 42.3 (CH_2), 41.9 (CH_2), 41.7 (CH_2), 31.1 (CH), 30.2 (CH_3), 30.0 (CH_3), 21.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found: 274.1803.



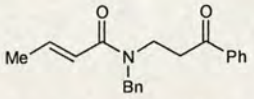
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenamide (131e)**. The title compound was prepared according to General

Procedure I from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and cinnamoyl chloride (4.03 g, 24.2 mmol) for a reaction time of 3 h. The product was purified by column chromatography (30% EtOAc/petrol) to give a yellow solid (2.10 g, 34%) as a 2:1 mixture of rotamers. m.p. 71-73 °C; IR ($CHCl_3$) 3027, 1713 (C=O), 1648 (C=C), 1426, 1203, 1161, 1028, 978, 764, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.79 (1H, d, J = 15.4 Hz, PhC**H**=), 7.61-7.26 (10H, m, Ar**H**), 6.86 (1H, d, J = 15.4 Hz, PhCH=C**H**), 4.80 (2H, s, C**H**$_2$Ph), 3.73 (2H, t, J = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.90 (2H, t, J = 6.7 Hz, C**H**$_2CH_2N$), 2.17 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.85 (1H, d, J = 15.3 Hz, PhC**H**=), 7.61-7.26 (10H, m, Ar**H**), 7.01 (1H, d, J = 15.3 Hz, PhCH=C**H**), 4.76 (2H, s, C**H**$_2$Ph), 3.76 (2H, t, J = 7.1 Hz, $CH_2C\mathbf{H}_2N$), 2.74 (2H, t, J = 7.1 Hz, C**H**$_2CH_2N$), 2.13 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.4 (C), 206.0 (C), 167.0 (C), 166.4 (C), 143.5 (CH), 143.1 (CH), 137.5 (C), 137.0 (C), 135.0 (C), 129.6 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.3 (CH), 126.4 (CH), 117.1 (CH), 116.9 (CH), 52.3 (CH_2), 49.5 (CH_2), 42.9 (CH_2), 42.6 (CH_2), 41.8 (2 x CH_2), 30.2 (CH_3), 30.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{21}NO_2$ $[M+Na]^+$: 330.1465, found: 330.1465.

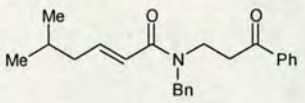


***N*-benzyl-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (131f)**. The title compound was prepared according to General Procedure I from methyl vinyl ketone (0.94 mL, 11.0 mmol), benzylamine (1.09 mL, 10.0 mmol) and the acid chloride (prepared according General Procedure A) derived from (2-furyl)acrylic acid (1.67 g, 12.1 mmol) for a reaction time of 14 h. The product was purified by column chromatography (40% EtOAc/petrol) to give an orange/red oil (1.56 g, 53%) as a 2:1 mixture of rotamers. IR (film) 2923, 1713 (C=O), 1650 (C=C), 1423, 1214, 1161, 1016, 815, 732, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.55 (1H, d, J = 15.1 Hz, C**H**=CHC=O), 7.50-7.24 (6H, m, Ar**H** and C**H**), 6.78 (1H, d, J = 15.1 Hz, CH=C**H**C=O), 6.58 (1H, bs, C**H**), 6.46-6.45 (1H, m, C**H**), 4.77 (2H, s, C**H**$_2$Ph), 3.69 (2H, t, J = 6.4 Hz, $CH_2C\mathbf{H}_2N$), 2.87 (2H, t, J = 6.4 Hz, C**H**$_2CH_2N$), 2.15 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.61 (1H, d, J = 15.2 Hz, C**H**=CHC=O), 7.50-7.24 (6H, m, Ar**H** and C**H**), 6.84 (1H, d, J = 15.2 Hz, CH=C**H**C=O), 6.62-6.58 (1H, m, C**H**), 6.50-6.49 (1H, m, C**H**), 4.74 (2H, s,

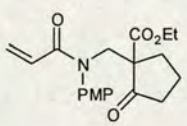
C**H**$_2$Ar), 3.71 (2H, t, J = 6.9 Hz, CH$_2$C**H**$_2$N), 2.74 (2H, t, J = 6.9 Hz, C**H**$_2$CH$_2$N), 2.13 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.5 (C), 206.1 (C), 166.9 (C), 166.3 (C), 151.5 (C), 143.9 (CH), 137.6 (C), 137.1 (C), 130.3 (CH), 129.9 (CH), 128.8 (CH), 128.6 (CH), 128.0 (CH), 127.6 (CH), 127.4 (CH), 126.6 (CH), 114.6 (CH), 114.3 (CH), 114.2 (CH), 114.0 (CH), 112.1 (CH) 52.2 (CH$_2$), 49.6 (CH$_2$), 43.1 (CH$_2$), 42.5 (CH$_2$), 41.9 (CH$_2$), 30.2 (CH$_3$), 30.0 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1441.



***N*-Benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-but-2-enamide (131g).** The title compound was prepared according to General Procedure J from 3-chloropropiophenone (927 mg, 5.50 mmol), benzylamine (0.55 mL, 5.0 mmol) and crotonoyl chloride (0.72 mL, 7.5 mmol) for a reaction time of 5 h. The product was purified by column chromatography (20% EtOAc/$CHCl_3$) to give a colorless gum (1.27 g, 86%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.96 (2H, d, J = 6.7 Hz, Ar**H**), 7.60-7.53 (1H, m, Ar**H**), 7.47-7.43 (2H, m, Ar**H**), 7.38-7.20 (5H, m, Ar**H**), 7.11-6.95 (1H, m, CH$_3$C**H**=), 6.24 (1H, dq, J = 14.9, 1.4 Hz, CH$_3$CH=C**H**), 4.72 (2H, s, C**H**$_2$Ph), 3.79 (2H, t, J = 6.8 Hz, CH$_2$C**H**$_2$N), 3.37 (2H, t, J = 6.8 Hz, C**H**$_2$CH$_2$N), 1.82 (3H, dd, J = 6.8, 1.4 Hz, C**H**$_3$CH=); (Minor rotamer) δ 7.85 (2H, d, J = 6.7 Hz, Ar**H**), 7.60-7.53 (1H, m, Ar**H**), 7.47-7.43 (2H, m, Ar**H**), 7.38-7.20 (5H, m, Ar**H**), 7.11-6.95 (1H, m, CH$_3$C**H**=), 6.36 (1H, d, J = 14.6 Hz, CH$_3$CH=C**H**), 4.71 (2H, s, C**H**$_2$Ph), 3.79 (2H, t, J = 7.4 Hz, CH$_2$C**H**$_2$N), 3.17 (2H, t, J = 6.8 Hz, C**H**$_2$CH$_2$N), 1.91 (3H, d, J = 6.5, 1.4 Hz, C**H**$_3$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 198.9 (C), 197.7 (C), 167.3 (C), 166.5 (C), 143.0 (CH), 142.4 (CH), 137.7 (C), 137.2 (C), 136.5 (C), 136.2 (C), 133.5 (CH), 133.1 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 121.6 (CH), 121.2 (CH), 52.3 (CH$_2$), 49.3 (CH$_2$), 43.2 (CH$_2$), 42.5 (CH$_2$), 38.0 (CH$_2$), 37.2 (CH$_3$), 18.1 (CH$_3$); IR ($CHCl_3$) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm^{-1}; HRMS (ES) Exact mass calcd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1645, found: 308.1643.

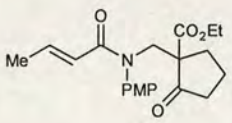


_N_-benzyl-_N_-(3-oxo-3-phenylpropyl)-(_E_)-5-methylhex-2-enamide (131h). The title compound was prepared according to General Procedure J from 3-chloropropiophenone (1.85 mg, 11.0 mmol), benzylamine (1.10 mL, 10.0 mmol) and the acid chloride (prepared according to General Procedure A) derived from (_E_)-5-methylhex-2-enoic acid (1.92 g, 15.0 mmol) for a reaction time of 15 h. The product was purified by column chromatography (15% EtOAc/$CHCl_3$) to give a yellow oil (1.62 g, 46%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2955, 1680 (C=O), 1656 (C=C), 1447, 1368, 1211, 1028, 980, 844, 742 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 8.02-8.00 (2H, m, Ar**H**), 7.62-7.58 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 7.41-7.24 (5H, m, Ar**H**), 7.01 (1H, dt, J = 15.0, 7.5 Hz, CH_2CH=), 6.24 (1H, d, J = 15.0 Hz, CH_2CH=C**H**), 4.76 (2H, s, C**H**$_2$Ph), 3.83 (2H, t, J = 6.8 Hz, CH_2CH_2N), 3.41 (2H, t, J = 6.8 Hz, C**H**$_2CH_2N$), 2.10-2.06 (2H, m, C**H**$_2CH$=), 1.86-1.68 (1H, m, $(CH_3)_2$C**H**), 0.92 (6H, d, J = 6.8 Hz, (C**H**$_3)_2CH$); (Minor rotamer) δ 7.88 (2H, d, J = 15.0 Hz, Ar**H**), 7.64-7.58 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 7.41-7.24 (5H, m, Ar**H**), 7.08 (1H, dt, J = 14.9, 7.4 Hz, CH_2CH=), 6.35 (1H, d, J = 14.9 Hz, CH_2CH=C**H**), 4.75 (2H, s, C**H**$_2$Ph), 3.83 (2H, t, J = 7.4 Hz, CH_2CH_2N), 3.21 (2H, t, J = 7.4 Hz, C**H**$_2CH_2N$), 2.18-2.14 (2H, m, C**H**$_2CH$=), 1.86-1.68 (1H, m, $(CH_3)_2$C**H**), 0.97 (6H, d, J= 6.6 Hz, (C**H**$_3)_2CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 198.9 (C), 197.6 (C), 167.3 (C), 166.5 (C), 146.8 (CH), 146.1 (CH), 137.7 (C), 137.2 (C), 136.5 (C), 136.2 (C), 133.4 (CH), 133.1 (CH), 128.7 (CH), 128.5 (CH), 128.0 (CH), 127.8 (CH), 127.4 (CH), 127.3 (CH), 126.4 (CH), 121.1 (CH), 120.7 (CH), 52.3 (CH_2), 49.3 (CH_2), 43.3 (CH_2), 42.5 (CH_2), 41.7 (CH_2), 41.6 (CH_2), 38.0 (CH_2), 37.2 (CH_2), 27.8 (CH), 22.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{28}NO_2$ $[M+H]^+$: 350.2115, found: 350.2114.

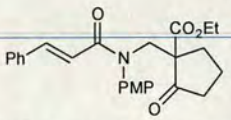


1-[_N_-Acryloyl-_N_-(4-methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (131i). The title compound was prepared by General Procedure D from the amine **166** (2.33 g, 8.00 mmol) and acryloyl chloride (1.02 mL, 12.0 mmol) for a reaction time of 65 h and purified by column chromatography (40% EtOAc/petrol) to give a pale brown oil (1.78 g, 64%). IR (film) 2977, 1751 (C=O), 1721 (C=O), 1659 (C=O),

1618, 1511, 1408, 1249, 1173, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.10 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.88-6.87 (2H, m, Ar**H**), 6.30 (1H, dd, *J* = 16.8, 2.0 Hz, C**H**$_2$=), 5.97 (1H, dd, *J* = 16.8, 10.3 Hz, CH_2=C**H**), 5.50 (1H, dd, *J* = 10.3, 2.0 Hz, C**H**$_2$=), 4.30 (2H, d, *J* = 5.2 Hz, C**H**$_2$N), 3.86-3.78 (1H, m, OC**H**$_2$$CH_3$), 3.81 (3H, s, OC**H**$_3$), 3.72-3.63 (1H, m, OC**H**$_2$$CH_3$), 2.54-2.27 (3H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 2.19-1.97 (3H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 1.01 (3H t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 212.3 (C), 169.6 (C), 166.7 (C), 159.0 (C), 134.0 (C), 129.5 (2 x CH), 128.0 (CH and CH_2), 114.4 (2 x CH), 61.5 (CH_2), 60.7 (C), 55.4 (CH_3), 50.9 (CH_2), 38.1 (CH_2), 31.6 (CH_2), 19.5 (CH_2), 13.7 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{24}NO_5$ $[M+H]^+$: 346.1650, found: 346.1644.

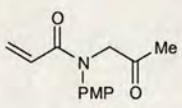


1-[*N*-(*E*)-But-2-enoyl-*N*-(4-methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (131j). The title compound was prepared by General Procedure D from the amine **166** (295 mg, 1.00 mmol) and crotonoyl chloride (143 μL, 1.50 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a pale brown oil (307 mg, 84%). IR (film) 2965, 1750 (C=O), 1719 (C=O), 1666 (C=O), 1629, 1510, 1445, 1289, 1249, 1029 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.09 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.92-6.82 (3H, m, Ar**H** and CH_3C**H**=), 5.65 (1H, dq, *J* = 15.1, 1.7 Hz, CH_3CH=C**H**), 4.33 (1H, d, *J* = 13.9 Hz, C**H**$_2$N), 4.25 (1H, d, *J* =13.9 Hz, C**H**$_2$N), 3.87-3.78 (1H, m, OC**H**$_2$$CH_3$), 3.83 (3H, s, OC**H**$_3$), 3.72-3.63 (1H, m, OC**H**$_2$$CH_3$), 2.55-1.97 (6H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 1.71 (3H, dd, *J*= 6.9, 1.7 Hz, C**H**$_3$CH=), 1.01 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 212.4 (C), 169.6 (C), 167.0 (C), 158.9 (C), 142.0 (CH), 134.3 (C), 129.5 (2 x CH), 122.2 (CH), 114.3 (2 x CH), 61.4 (CH_2), 60.8 (C), 55.4 (CH_3), 50.8 (CH_2), 38.1 (CH_2), 31.5 (CH_2), 19.5 (CH_2), 18.0 (CH_3), 13.7 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{26}NO_5$ $[M+H]^+$: 360.1806, found: 360.1809.

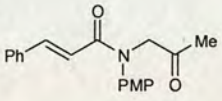


1-[*N*-(4-Methoxyphenyl)-*N*-((*E*)-3-phenylacryloyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (131k). The title compound was prepared by General Procedure D from the amine **166** (2.33 g, 8.00 mmol) and cinnamoyl

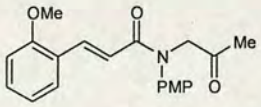
chloride (2.04 g, 12.0 mmol) for a reaction time of 65 h and purified by column chromatography (10% EtOAc/petrol→30% EtOAc/petrol) to give a pale brown gum (2.19 g, 65%). IR (film) 2961, 1750 (C=O), 1720 (C=O), 1655 (C=O), 1616, 1510, 1249, 1029, 839, 806 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.62 (1H, d, J = 15.6 Hz, PhC**H**=), 7.29 (5H, br s, Ar**H**), 7.16 (2H, app d, J = 7.8 Hz, Ar**H**), 6.92 (2H, d, J = 9.1 Hz, Ar**H**), 6.27 (1H, d, J = 15.6 Hz, PhCH=C**H**), 4.40 (1H, d, J = 13.9 Hz, C**H**$_2$N), 4.34 (1H, d, J = 13.9 Hz, C**H**$_2$N), 3.90-3.81 (1H, m, OC**H**$_2$CH$_3$), 3.85 (3H, s, OC**H**$_3$), 3.77- 3.67 (1H, m, OC**H**$_2$CH$_3$), 2.58-2.30 (3H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 2.24-2.13 (2H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 2.09-1.98 (1H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 1.04 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 212.5 (C), 169.6 (C), 167.1 (C), 159.0 (C), 142.5 (CH), 135.0 (C), 134.1 (C), 129.6 (2 x CH), 128.6 (2 x CH), 127.9 (2 x CH), 118.1 (CH), 114.4 (2 x CH), 61.5 (CH_2), 60.9 (C), 55.5 (CH_3), 51.0 (CH_2), 38.2 (CH_2), 31.6 (CH_2), 19.6 (CH_2), 13.7 (CH_3); LRMS (ES) Mass calcd for $C_{25}H_{28}NO_5$ $[M+H]^+$: 422.2, found: 422.0.



***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)propenamide (113a).** Prepared according to a previously reported procedure (Chapter 3.3).

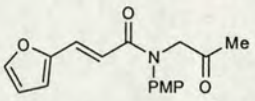


***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-phenylpropenamide (113c)**. Prepared according to a previously reported procedure (Chapter 3.3).

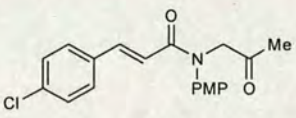


***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-(2-methoxyphenyl)propenamide (131l)**. The title compound was prepared according to General Procedure D from the amine **126** (537 mg, 3.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from 2-methoxycinnamic acid (801 mg, 4.30 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a beige solid (617 mg, 61%). m.p. 111-112 °C; IR ($CHCl_3$) 2935, 1733 (C=O), 1652 (C=O), 1613, 1510, 1376, 1248, 1070, 1028, 755 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.97 (1H, d, J = 15.7 Hz, ArC**H**=),

7.30-7.24 (4H, m, Ar**H**), 6.93 (2H, dd, J = 8.9 Hz, Ar**H**), 6.88-6.83 (2H, m, Ar**H**), 6.52 (1H, d, J = 15.7 Hz, ArCH=C**H**), 4.53 (2H, s, C**H**$_2$N), 3.85 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 2.22 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.7 (C), 166.8 (C), 158.9 (C), 158.1 (C), 137.8 (CH), 135.9 (C), 130.7 (CH), 129.2 (2 x CH), 128.7 (CH), 124.0 (C), 120.4 (CH), 118.5 (CH), 114.5 (2 x CH), 110.9 (CH), 59.7 (CH_2), 55.4 (CH_3), 55.2 (CH_3), 27.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$: 340.1544, found: 340.1549.

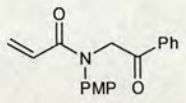


***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-furan-2-ylpropenamide (131m).** The title compound was prepared according to General Procedure D from the amine **126** (1.07 g, 6.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from 3-(2-furyl)acrylic acid (1.24 mg, 9.00 mmol) for a reaction time of 24 h and purified by recrystallisation (30% EtOAc/petrol) to give brown needles (590 mg, 33%). m.p. 103-104 °C; IR ($CHCl_3$) 2918, 1733 (C=O), 1655 (C=O), 1615, 1511, 1374, 1250, 1171, 1017, 840 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.46 (1H, d, J = 15.3 Hz, ArC**H**=CH), 7.37 (1H, d, J = 1.7 Hz, Ar**H**), 7.28 (2H, d, J = 8.9 Hz, Ar**H**), 6.95 (2H, d, J = 8.9 Hz, Ar**H**), 6.53 (1H, d, J = 3.4 Hz, ArCH=C**H**), 6.31 (1H, d, J = 15.3 Hz, ArCH=C**H**), 4.54 (2H, s, C**H**$_2$N), 3.87 (3H, s, OC**H**$_3$), 2.23 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.5 (C), 166.3 (C), 159.0 (C), 151.5 (C), 144.0 (CH), 135.2 (C), 129.1 (2 x CH), 115.4 (CH), 114.7 (2 x CH), 114.0 (CH), 112.0 (CH), 59.9 (CH_2), 55.4 (CH_3), 27.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{17}H_{17}NO_4$ $[M+H]^+$: 300.1230, found: 300.1229.

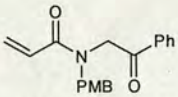


***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-(4-chlorophenyl)propenamide (131n).** The title compound was prepared according to General Procedure D from the amine **126** (1.07 g, 6.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from 4-chlorocinammic acid (1.64 mg, 9.00 mmol) for a reaction time of 24 h and purified by recrystallisation (EtOH) to give a beige micro crystalline solid (756 mg, 37%). m.p. 119-120 °C; IR ($CHCl_3$) 2924, 1732 (C=O), 1654 (C=O), 1616, 1511, 1491, 1378, 1250, 980 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ

7.63 (1H, d, J = 15.6 Hz, ArC**H**=CH), 7.28 (2H, d, J = 9.0 Hz, Ar**H**), 6.95 (2H, d, J = 9.0 Hz, Ar**H**), 6.38 (1H, d, J = 15.6 Hz, ArCH=C**H**), 4.55 (2H, s, C**H**$_2$N), 3.87 (3H, s, OC**H**$_3$), 2.23 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 202.4 (C), 166.1 (C), 159.1 (C), 141.1 (C), 135.4 (CH), 135.4 (C), 135.1 (C), 133.5 (C), 129.2 (2 x CH), 129.1 (CH), 128.9 (CH), 118.3 (CH), 114.7 (2 x CH), 59.9 (CH_2), 55.5 (CH_3), 27.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{18}ClNO_3$ $[M+H]^+$: 344.1048, found: 344.1049.

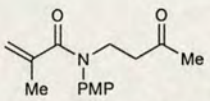


***N*-(4-Methoxyphenyl)-*N*-(2-oxo-2-phenylethyl)propenamide (133a)**. The title compound was prepared according to general procedure D from the amine **167** (1.00 g, 4.12 mmol) and acryloyl chloride (500 μL, 6.10 mmol) for a reaction time of 20 h and purified by column chromatography (40% EtOAc/petrol) to give a yellow solid (790 mg, 65%). m.p. 78-80 °C; IR ($CHCl_3$) 2925, 1699 (C=O), 1655 (C=C), 1509, 1421, 1248, 1221, 979, 754 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.00-7.97 (2H, m, Ar**H**), 7.61-7.57 (1H, m, Ar**H**), 7.50-7.45 (2H, m, Ar**H**), 7.33 (2H, dm, J = 8.9 Hz, Ar**H**), 6.93 (2H, dm, J = 9.0 Hz, Ar**H**), 6.42 (1H, dd, J = 16.8, 2.1 Hz, C**H**$_2$=), 6.21 (1H, dd, J = 16.8, 10.3 Hz, CH_2=C**H**), 5.60 (1H, dd, J = 10.3, 2.1 Hz, C**H**$_2$=), 5.18 (2H, s, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 193.4 (C), 166.0 (C), 159.0 (C), 135.1 (C), 135.0 (C), 133.4 (2 x CH), 129.4 (2 x CH), 128.6 (2 x CH_2), 128.0 (CH), 127.9 (2 x CH), 127.8 (CH), 114.5 (2 x CH), 56.4 (CH_2), 55.4 (CH_3); HRMS (FAB) Exact mass calcd for $C_{18}H_{18}NO_3$ $[M+H]^+$: 296.1282, found: 296.1286.

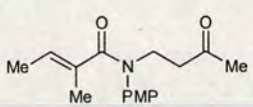


***N*-(4-Methoxybenzyl)-*N*-(2-oxo-2-phenylethyl)propenamide (133b)**. The title compound was prepared according to general procedure D from the amine hydrochloride **168** (870 mg, 3.00 mmol) and acryloyl chloride (360 μL, 4.48 mmol) for a reaction time of 20 h and purified by column chromatography (40% EtOAc/petrol) to give a pale yellow solid (650 mg, 46%) as a 3:1 mixture of rotamers. m.p. 78-80 °C; IR ($CHCl_3$) 2930, 1698 (C=O), 1650 (C=C), 1512, 1448, 1247, 1031, 754 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.95-7.93 (2H, m, Ar**H**), 7.62-7.56 (1H, m, Ar**H**), 7.50-7.43 (2H, m, Ar**H**), 7.16-7.14 (2H, m, Ar**H**), 6.90-6.88 (2H m, Ar**H**), 6.72 (1H, dd, J = 16.7, 10.4 Hz, CH_2=C**H**),

6.45 (1H, dd, J = 16.7, 1.9 Hz, C**H**$_2$=), 5.77 (1H, dd, J = 10.4, 1.9 Hz, C**H**$_2$=), 4.81 (2H, s, NC**H**$_2$C=O), 4.68 (2H, s, C**H**$_2$Ar), 3.80 (3H, s, OC**H**$_3$); (Minor rotamer) δ 7.89-7.86 (2H, m, Ar**H**), 7.62-7.60 (1H, m, Ar**H**), 7.50-7.43 (2H, m, Ar**H**), 7.21-7.13 (2H, m, Ar**H**), 6.86-6.83 (2H, m, Ar**H**), 6.40 (1H, dd, J = 16.7, 2.2 Hz, C**H**$_2$=), 6.29 (1H, dd, J = 16.7, 10.1 Hz, CH$_2$=C**H**), 5.66 (1H, dd, J = 10.1, 2.2 Hz, C**H**$_2$=), 4.81 (2H, s, NC**H**$_2$C=O), 4.69 (2H, s, C**H**$_2$Ar), 3.78 (3H, s, OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 194.1 (C), 193.5 (C), 167.4 (C), 167.2 (C), 159.3 (C), 159.1 (C), 135.2 (C), 134.6 (C), 134.0 (C), 133.5 (CH), 129.9 (CH), 129.2 (CH$_2$), 128.9 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH$_2$), 128.1 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 114.3 (CH), 114.3 (CH), 55.3 (CH$_3$), 52.5 (CH$_3$), 51.5 (CH$_2$), 49.4 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$: 310.1438, found: 310.1438.



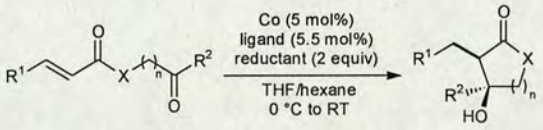
***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-2-methylpropenamide (137a)**. The title compound was prepared according to General Procedure D from the amine **118** (1.00 g, 5.20 mmol) and methacryloyl chloride (755 μL, 7.80 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give an orange/brown solid (976 mg, 72%). m.p. 64-65 °C; IR ($CHCl_3$) 2954, 1713 (C=O), 1651 (C=O), 1626, 1512, 1371, 1249, 1182, 1031, 836 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.01 (2H, d, J = 8.8 Hz, Ar**H**), 6.83 (2H, d, J = 8.8 Hz, Ar**H**), 5.00 (1H, s, C**H**=), 4.97 (1H, s, C**H**=), 3.96 (2H, t, J = 7.4 Hz, C**H**$_2$N), 3.79 (3H, s, OC**H**$_3$), 2.72 (2H, t, J = 7.4 Hz, C**H**$_2$CH$_2$N), 2.11 (3H, s, C**H**$_3$C=O), 1.69 (3H, s, =CC**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 207.0 (C), 172.0 (C), 158.5 (C), 140.7 (C), 135.4 (C), 128.6 (2 x CH), 119.3 (CH$_2$), 114.4 (2 x CH), 55.4 (CH$_3$), 45.2 (CH$_2$), 41.2 (CH$_2$), 30.0 (CH$_3$), 20.2 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{15}H_{20}NO_3$ $[M+H]^+$: 262.1438, found: 262.1438.



***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-2-methylbut-2-enamide (137b)**. The title compound was prepared according to General Procedure D from the amine **118** (965 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure A) from tiglic acid (613 mg, 6.00 mmol) for a reaction time of 18 h and purified by column

chromatography (30% EtOAc/petrol) to give an orange/brown oil (500 mg, 36%). IR ($CHCl_3$) 3489 (OH), 2961, 1732 (C=O), 1660 (C=O), 1513, 1380, 1251, 1171, 841, 606 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.98 (2H, d, J = 9.0 Hz, Ar**H**), 6.82 (2H, d, J = 9.0 Hz, Ar**H**), 5.77-5.70 (1H, m, $CH_3C\mathbf{H}$=C), 3.95 (2H, t, J = 7.4 Hz, $C\mathbf{H}_2N$), 3.79 (3H, s, $OC\mathbf{H}_3$), 2.72 (2H, t, J = 7.4 Hz, $C\mathbf{H}_2CH_2N$), 2.11 (3H, s, J = 6.8 Hz, $C\mathbf{H}_3C$=O), 1.48 (3H, s, =$C(C\mathbf{H})_3C$=O), 1.49-1.45 (3H, m, $C\mathbf{H}_3CH$=); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 207.1 (C), 173.3 (C), 158.1 (C), 135.8 (C), 132.7 (C), 130.4 (CH), 128.5 (2 x CH), 114.3 (2 x CH), 55.3 (CH_3), 45.4 (CH_2), 41.3 (CH_2), 30.0 (CH_3), 13.9 (CH_3), 13.2 (CH_3).

Cobalt-Catalyzed Reductive Aldol Cyclizations



Using $Co(acac)_2/Et_2Zn$: General Procedure K

A solution of the substrate (0.20 mmol) and $Co(acac)_2 \cdot 2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Using $CoCl_2/Cy_2PPh/Et_2Zn$: General Procedure L

A solution of the substrate (0.20 mmol), $CoCl_2$ (1.3 mg, 0.01 mmol) and Cy_2PPh (3.0 mg, 0.011 mmol) in THF (1.5 mL) was stirred at room temperature for 30 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as

observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Using $Co(acac)_2/Et_3Al$: General Procedure M

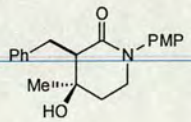
A solution of the substrate (0.20 mmol) and $Co(acac)_2 \cdot 2H_2O$ (2.6 mg, 0.01 mmol) in THF (3 mL) was stirred at room temperature for 15 min. The mixture was cooled 0 °C and Et_3Al (1 M solution in hexane, 0.40 mL, 0.40 mmol) was added dropwise over 5 min. The reaction was stirred at 0° C for 1 h and then at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched carefully by the addition of 1 M HCl (5 mL). The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.

Workup A

The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.

Workup B

The reaction was quenched carefully with saturated aqueous NH_4Cl solution (10 mL) and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclized product.

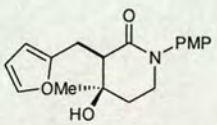


(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (90l). *On a 0.20 mmol scale:* The title compound was prepared according to General Procedure K from **89l** (65 mg, 0.20 mmol) for a reaction time of 4 h followed by Workup A and

purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (58 mg, 89%).

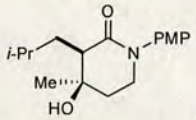
On a 5.00 mmol scale: A solution of **89l** (1.62 g, 5.00 mmol) and $Co(acac)_2 \cdot 2H_2O$ (6.4 mg, 0.025 mmol) in THF (10 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 10.0 mL, 10.0 mmol) was then added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h and then at room temperature for 2.5 h. The reaction was filtered through a short pad of SiO_2 (*ca.* 5 cm high x 3 cm diameter) using EtOAc (200 mL) as eluent and the filtrate was concentrated *invacu o*. Purification of the residue by column chromatography (30% EtOAc/$CHCl_3$) gave the *lactam* **90l** (1.28 g, 79%) as a white solid.

m.p. 156-157 °C; IR ($CHCl_3$) 3409, 2935, 1630 (C=O), 1605, 1511, 1442, 1334, 1245, 1141, 1033 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38 (2H, d, J = 7.3 Hz, Ar**H**), 7.27 (2H, t, J = 7.5 Hz, Ar**H**), 7.18 (1H, d, J = 7.3 Hz, Ar**H**), 7.15 (2H, d, J = 9.0 Hz, Ar**H**), 6.90 (2H, dm, J = 9.0 Hz, Ar**H**), 3.82 (1H, ddd, J = 12.1, 7.4, 7.4 Hz, CH_2CH_2N), 3.84 (3H, s, OCH_3), 3.41 (1H, ddd, J = 10.5, 5.3, 5.3 Hz, CH_2CH_2N), 3.34 (1H, dd, J = 14.5, 5.3 Hz, CH_2CH), 3.14 (1H, dd, J = 14.5, 5.3 Hz, CH_2CH), 2.72 (1H, t, J = 5.3 Hz, CH_2CH), 1.95 (2H, app dd, J = 7.4, 5.3 Hz, CH_2CH_2N), 1.79 (1H, s, O**H**), 1.34 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.4 (C), 158.0 (C), 142.1 (C), 136.2 (C), 129.2 (2 x CH), 128.4 (2 x CH), 127.4 (2 x CH), 125.9 (CH), 114.4 (2 x CH), 71.1 (C), 55.4 (CH_3), 54.6 (CH), 47.3 (CH_2), 36.1 (CH_2), 32.3 (CH_2), 29.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{23}NO_3Na$ $[M+Na]^+$: 348.1570, found: 348.1571.

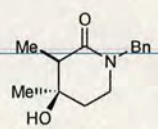


(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (132a). The title compound was prepared according to General Procedure K from **131a** (63 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (57 mg, 90%). m.p. 150-152 °C; IR (film) 3410, 2934, 1631 (C=O), 1604, 1511,

1442, 1297, 1244, 1145, 1033 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33 (1H, dd, J = 1.9, 0.8 Hz, C**H**), 7.14 (2H, dm, J = 9.0 Hz, Ar**H**), 6.90 (2H, dm, J = 9.0 Hz, Ar**H**), 6.31 (1H, dd, J = 3.2, 1.9 Hz, C**H**), 6.16 (1H, dd, J = 3.2, 0.8 Hz, C**H**), 3.84 (1H, ddd, J= 12.2, 10.0, 5.2 Hz, CH_2CH_2N), 3.80 (3H, s, OCH_3), 3.45-3.39 (1H, m, CH_2CH_2N), 3.37 (1H, dd, J = 15.6, 5.0 Hz, CH_2CH), 3.25 (1H, dd, J = 15.6, 6.2 Hz, CH_2CH), 2.79 (1H, dd, J = 6.2, 5.0 Hz, CH_2CH), 2.18 (1H, s, O**H**), 2.02-1.94 (1H, m, CH_2CH_2N), 1.88 (1H, dt, J = 13.7, 4.9 Hz, CH_2CH_2N), 1.32 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.5 (C), 158.0 (C), 154.5 (C), 140.6 (CH), 136.2 (C), 127.3 (2 x CH), 114.4 (2 x CH), 110.9 (CH), 107.0 (CH), 70.3 (C), 55.4 (CH_3), 51.8 (CH), 47.2 (CH_2), 36.2 (CH_2), 28.6 (CH_3), 24.8 (CH_2); HRMS (FAB) Exact mass calcd for $C_{18}H_{22}NO_4$ $[M+H]^+$: 316.1543, found: 316.1542.

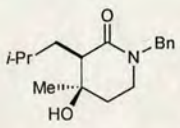


(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (132b). The title compound was prepared according to General Procedure K from **131b** (58 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (20% EtOAc/$CHCl_3$) to give a white solid (45 mg, 78%). m.p. 120 °C; IR (film) 3416, 2954, 1631 (C=O), 1605, 1512, 1442, 1297, 1244, 1143, 1034 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.14 (1H, d, J = 9.0 Hz, Ar**H**), 6.90 (2H, d, J = 9.0 Hz, Ar**H**), 3.83 (1H, ddd, J = 12.1, 8.5, 5.6 Hz, CH_2CH_2N), 3.80 (3H, s, OCH_3), 3.47 (1H, dt, J = 8.3, 2.6 CH_2CH_2N), 2.10-1.94 (1H, m, CH_2CH_2N), 1.82 (1H, ddd, J = 13.4, 8.3, 4.7 Hz), 1.39 (3H, s, CH_3COH), 0.97 (3H, d, J = 6.7 Hz $CH(CH_3)_2$), 0.95 (3H, d, J = 6.7 Hz $CH(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.6 (C), 158.0 (C), 136.2 (C), 127.4 (2 x CH), 114.4 (2 x CH), 70.9 (C), 55.5 (CH), 50.4 (CH), 47.3 (CH_2), 35.9 (CH_2), 35.3 (CH_2), 28.5 (CH_3), 27.8 (CH), 23.5 (CH_3), 21.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{25}NO_3$ $[M+H]^+$: 292.1907, found: 292.1905.

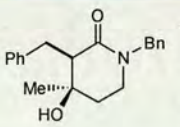


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3,4-dimethylpiperidin-2-one (132c). The title compound was prepared according to General Procedure K from **131c** (46 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (80%

EtOAc/petrol) to give a white solid (41 mg, 88%). m.p.155-157 °C; IR ($CHCl_3$) 3335 (OH), 2980, 1605 (C=O), 1496, 1509, 1360, 1236, 1196, 927, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.22 (5H, m, Ar**H**), 4.76 (1H, d, J = 14.8 Hz, C**H**$_2$Ph), 4.40 (1H, d, J = 14.8 Hz, C**H**$_2$Ph), 3.44 (1H, ddd, J = 12.1, 10.2, 5.3 Hz, CH_2C**H**$_2$N), 3.09 (1H, ddd, J = 12.1, 6.1, 3.9 Hz, CH_2C**H**$_2$N), 2.38 (1H, q, J = 7.3 Hz, CH_3C**H**), 1.99 (1H, br s, O**H**), 1.90 (1H, ddd, J = 13.6, 5.3, 3.9 Hz, C**H**$_2$$CH_2$N), 1.79 (1H, ddd, J = 13.6, 10.2, 6.1 Hz, C**H**$_2$$CH_2$N), 1.33 (3H, d, J = 7.3 Hz, C**H**$_3$CH), 1.31 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.7 (C), 137.2 (C), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 69.9 (C), 50.2 (CH_2), 46.7 (CH), 42.9 (CH_2), 34.8 (CH_2), 28.3 (CH_3), 10.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{19}NO_2$ $[M+H]^+$: 234.1489, found: 234.1491.

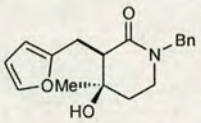


(±)-(3*R*,4*R*)-1-Benzyl-3-*iso*-butyl-4-hydroxy-4-methylpiperidin-2-one (132d). The title compound was prepared according to General Procedure K from **131d** (55 mg, 0.20 mmol) for a reaction time of 8 h using Workup A and purified by column chromatography (50% EtOAc/petrol) to give a white solid (55 mg, >99%). m.p. 113-115 °C; IR ($CHCl_3$) 3407 (OH), 2954, 1620 (C=O), 1495, 1452, 1267, 1150, 1116, 732, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.27 (5H, m, Ar**H**), 4.72 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 4.49 (1H, d, J = 14.8 Hz, C**H**$_2$Ph), 3.41 (1H, ddd, J = 12.3, 7.9, 5.8 Hz, CH_2C**H**$_2$N), 3.15-3.08 (1H, m, CH_2C**H**$_2$N), 2.32 (1H, dd, J = 8.2, 2.8 Hz, CH_2C**H**), 2.11-1.93 (2H, m), 1.84-1.71 (3H, m) and 1.46 (1H, ddd, J= 13.6, 9.2, 3.0 Hz, C**H**$_2$$CH_2$N, $(CH_3)_2$C**H**C**H**$_2$ and O**H**), 1.32 (3H, s, C**H**$_3$COH), 1.03 (3H, d, J = 6.7 Hz, $(CH_3)_2$CH), 0.99 (3H, d, J = 6.7 Hz, $(CH_3)_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.3 (C), 137.3 (C), 128.5 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 127.9 (2 x CH), 127.2 (CH), 70.6 (C), 50.2 (CH), 50.0 (CH_2), 43.0 (CH_2), 36.4 (CH_2), 34.2 (CH_2), 28.2 (CH_3), 27.7 (CH), 23.5 (CH_3), 21.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{26}NO_2$ $[M+H]^+$: 276.1958, found: 276.1960.

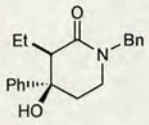


(±)-(3*R*,4*R*)-1,3-Dibenzyl-4-hydroxy-4-methylpiperidin-2-one (132e). The title compound was prepared according to General Procedure K from **131e** (61 mg, 0.20 mmol) for a reaction time of 8 h

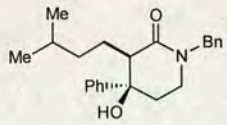
followed by Workup A and purification by column chromatography (60% EtOAc/petrol) to give a white solid (60 mg, 97%). m.p. 137-139 °C; IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1452, 1353, 1267, 1030, 740, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44-7.41 (2H, m, Ar**H**), 7.39-7.28 (7H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.76 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 4.58 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 3.47 (1H, ddd, J = 12.2, 9.1, 5.6 Hz, CH_2C**H**$_2$N), 3.37 (1H, dd, J = 14.4, 5.4 Hz, C**H**$_2$CH), 3.23 (1H, dd, J = 14.4, 5.4 Hz, C**H**$_2$CH), 3.16-3.09 (1H, m, CH_2C**H**$_2$N), 2.73 (1H, t, J = 5.4 Hz, CH_2C**H**), 1.92-1.78 (3H, m, C**H**$_2$$CH_2$N and O**H**), 1.31 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.1 (C), 141.9 (C), 137.1 (CH), 129.2 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.2 (C), 126.0 (C), 71.0 (C), 54.2 (CH), 50.4 (CH_2), 43.0 (CH_2), 35.2 (CH_2), 32.8 (CH_2), 28.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$: 310.1802, found: 310.1802.



(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-methylpiperidin-2-one (132f). The title compound was prepared according to General Procedure K from **131f** (59 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, >99%). m.p. 120-122 °C; IR ($CHCl_3$) 3409 (OH), 2925, 1620 (C=O), 1496, 1452, 1270, 1146, 1008, 731, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.26 (6H, m, Ar**H** and C**H**), 6.36-6.34 (1H, m, C**H**), 6.20-6.19 (1H, m, C**H**), 4.72 (1H, d, J = 14.7 Hz, NC**H**$_2$Ar), 4.57 (1H, d, J = 14.7 Hz, NC**H**$_2$Ar), 3.46 (1H, ddd, J = 12.1, 9.1, 5.9 Hz, CH_2C**H**$_2$N), 3.40 (1H, dd, J = 15.5, 4.9 Hz, C**H**$_2$CH), 3.32 (1H, dd, J = 15.5, 6.2 Hz, C**H**$_2$CH), 3.14-3.08 (1H, m, CH_2C**H**$_2$N), 2.76 (1H, app t, J = 5.6 Hz, CH_2C**H**), 2.11 (1H, br s, O**H**), 1.87-1.76 (2H, m, C**H**$_2$$CH_2$N), 1.29 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.1 (C), 154.5 (C), 140.7 (CH), 137.1 (C), 128.5 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 110.8 (CH), 106.9 (CH), 70.2 (C), 51.5 (CH), 50.4 (CH_2), 42.9 (CH_2), 35.5 (CH_2), 28.4 (CH_2), 25.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{22}NO_3$ $[M+H]^+$: 300.1594, found: 300.1593.

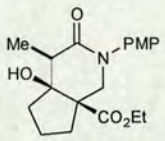


(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-phenylpiperidin-2-one (132g). The title compound was prepared according to General Procedure K from **131g** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (58 mg, 94%). m.p. 199-201 °C; IR ($CHCl_3$) 3384 (OH), 2948, 1604 (C=O), 1491, 1445, 1238, 1146, 755, 705, 682 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50-7.28 (10H, m, Ar**H**), 4.77 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 4.61 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 3.57 (1H, ddd, J = 12.1, 10.5, 5.2 Hz, CH_2C**H**$_2$N), 3.16 (1H, ddd, J = 12.1, 6.2, 3.5 Hz, CH_2C**H**$_2$N), 2.74 (1H, dd, J = 7.3, 3.4 Hz, CH_2C**H**), 2.26 (1H, ddd, J = 14.0, 10.5, 6.2 Hz, C**H**$_2$$CH_2$N), 2.01 (1H, ddd, J = 14.0, 5.2, 3.5 Hz, C**H**$_2$$CH_2$N), 1.98 (1H, br s, O**H**), 1.92-1.80 (1H, m, CH_3C**H**$_2$), 1.59-1.48 (1H, m, CH_3C**H**$_2$), 1.07 (3H, t, J = 7.4 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.8 (C), 145.9 (C), 137.3 (C), 128.6 (4 x CH), 127.9 (2 x CH), 127.3 (2 x CH), 124.5 (2 x CH), 75.6 (C), 52.7 (CH), 50.2 (CH_2), 43.3 (CH_2), 36.6 (CH_2), 20.2 (CH_2), 14.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_2$ $[M+H]^+$: 310.1802, found: 310.1803.

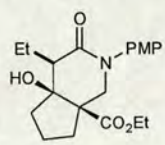


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-(3-methylbutyl)-4-phenylpiperidin-2-one (132h). The title compound was prepared according to General Procedure K from **131h** (70 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (66 mg, 94%). m.p. 134-136 °C; IR ($CHCl_3$) 3399 (OH), 2952, 1617 (C=O), 1494, 1451, 1353, 1242, 758, 733, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49-7.28 (10H, m, Ar**H**), 4.80 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 4.56 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 3.57 (1H, ddd, J = 12.1, 10.6, 5.2 Hz, CH_2C**H**$_2$N), 3.16 (1H, ddd, J = 12.1, 6.2, 3.5 Hz, CH_2C**H**$_2$N), 2.78 (1H, dd, J = 7.4, 3.1 Hz, C**H**C=O), 2.27 (1H, ddd, J = 14.0, 10.6, 6.2 Hz, C**H**$_2$$CH_2$N), 2.10 (1H, br s, O**H**), 2.02 (1H, ddd, J = 14.0, 5.2, 3.5 Hz, C**H**$_2$$CH_2$N), 1.87-1.77 (1H, m), 1.68-1.58 (1H, m), 1.48-1.38 (2H, m) and 1.15-1.05 (1H, m, $(CH_3)_2$C**H**C**H**$_2$C**H**$_2$), 0.78 (3H, d, J = 6.0 Hz, (CH_3)$_2$CH), 0.76 (3H, d, J = 6.0 Hz, (CH_3)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 145.8 (C), 137.2 (C), 128.5 (4 x CH), 127.9 (2 x CH), 127.2 (2 x CH), 124.6 (2 x CH), 75.4 (C), 51.5 (CH), 50.2

(CH_2), 43.3 (CH_2), 39.4 (CH_2), 36.3 (CH_2), 28.1 (CH), 24.6 (CH_2), 22.4 (CH_3), 22.2 (CH_3); HRMS (FAB) Exact mass calcd for $C_{23}H_{30}NO_2$ $[M+H]^+$: 352.2272, found: 352.2272.

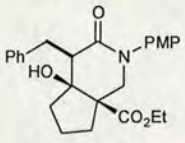


(±)-(1*R*,5*R*,6*S*)-1-Carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-5-methyl-3-azabicyclo[4.3.0]nonan-4-one (132i). The title compound was prepared according to General Procedure L from **131i** (69 mg, 0.20 mmol) for a reaction time of 3 h followed by Workup B and purification by column chromatography (50% EtOAc/petrol→60% EtOAc/petrol) to give a white solid (39 mg, 56%). m.p. 111-112 °C; IR ($CHCl_3$) 3434 (OH), 2941, 1724 (C=O), 1666 (C=O), 1512, 1465, 1443, 1246, 1033, 832 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20 (2H, dm, J = 9.0 Hz, Ar**H**), 6.87 (2H, dm, J = 9.0 Hz, Ar**H**), 4.14 (1H, d, J = 13.5 Hz, C**H**$_2$N), 4.15-4.09 (2H, m, OC**H**$_2$CH$_3$), 3.79 (3H, s, OC**H**$_3$), 3.6 (1H, d, J = 13.5 Hz, C**H**$_2$N), 3.21 (1H, s, O**H**), 2.68 (1H, q, J = 6.9 Hz, CH$_3$C**H**), 2.43-2.33 (1H, m, C**H**$_2$CH$_2$C**H**$_2$), 2.16-2.09 (1H, m, C**H**$_2$CH$_2$C**H**$_2$), 2.00-1.89 (2H, m, C**H**$_2$CH$_2$C**H**$_2$), 1.74-1.62 (2H, m, CH$_2$C**H**$_2$CH$_2$), 1.33 (3H, d, J = 6.9 Hz, C**H**$_3$CH), 1.11 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.8 (C), 171.6 (C), 157.4 (C), 135.7 (C), 126.4 (2 x CH), 113.8 (2 x CH), 85.5 (C), 61.5 (CH_2), 57.4 (C), 55.4 (CH_3), 54.6 (CH_2), 44.7 (CH), 40.8 (CH_2), 36.3 (CH_2), 23.1 (CH_2), 13.9 (CH_3), 9.4 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{26}NO_5$ $[M+H]^+$: 348.1806, found: 348.1805.

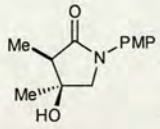


(±)-(1*R*,5*R*,6*S*)-1-Carbethoxy-5-ethyl-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (132j). The title compound was prepared according to General Procedure L from **131j** (72 mg, 0.20 mmol) for a reaction time of 1 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) to give a colorless oil (58 mg, 80%). IR (film) 3431 (OH), 2965, 1725 (C=O), 1666 (C=O), 1512, 1288, 1247, 1101, 1033, 836 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20 (2H, dm, J = 9.1 Hz, Ar**H**), 6.87 (2H, dm, J = 9.1 Hz, Ar**H**), 4.16 (1H, d, J = 13.6 Hz, C**H**$_2$N), 4.10 (2H, q, J = 7.2 Hz, OC**H**$_2$CH$_3$), 3.79 (3H, s, OC**H**$_3$), 3.61 (1H, d, J = 13.6 Hz, C**H**$_2$N), 3.27 (1H, br s, O**H**), 2.42-2.34 (2H, m), 2.17-2.03 (2H, m), 2.00-

1.91 (2H, m) and 1.78-1.62 (3H, m, CH_3CH_2CH and $CH_2CH_2CH_2$), 1.10 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.08 (3H, t, J = 7.4 Hz, CH_3CH_2CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 170.9 (C), 157.4 (C), 135.7 (C), 126.3 (2 x CH), 113.8 (2 x CH), 85.8 (C), 61.4 (CH_2), 57.8 (C), 55.4 (CH_3), 54.6 (CH_2), 53.2 (CH), 41.8 (CH_2), 36.6 (CH_2), 23.5 (CH_2), 18.3 (CH_2), 14.1 (CH_3), 13.9 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{28}NO_5$ $[M+H]^+$: 362.1963, found: 348.1962.

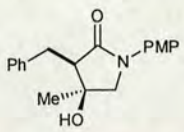


(±)-(1*R*,5*R*,6*S*)-5-Benzyl-1-carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (132k). The title compound was prepared by General Procedure L from **131k** (84 mg, 0.20 mmol) for a reaction time of 1 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol) to give a colorless oil (75 mg, 88%). IR (film) 3438 (OH), 2962, 1724 (C=O), 1671 (C=O), 1512, 1465, 1287, 1247, 1115, 832 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.36 (2H, m, Ar**H**), 7.29-7.24 (2H, m, Ar**H**), 7.21-7.15 (1H, m, Ar**H**), 7.18 (2H, dm, J = 9.1 Hz, Ar**H**), 6.86 (2H, dm, J = 9.1 Hz, Ar**H**), 4.11 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.11 (1H, d, J = 13.7 Hz, CH_2N), 3.79 (3H, s, OCH_3), 3.63 (1H, d, J = 13.7 Hz, CH_2N), 3.59 (1H, dd, J = 14.4, 8.1 Hz, CH_2CH), 3.51 (1H, s, O**H**), 2.96 (1H, dd, J = 14.4, 2.8 Hz, CH_2CH), 2.78 (1H, dd, J = 8.1, 2.8 Hz, CH_2CH), 2.40-2.23 (2H, m, CH_2CH_2CH), 2.05-1.91 (2H, m, $CH_2CH_2CH_2$), 1.73-1.62 (2H, m, $CH_2CH_2CH_2$), 1.08 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.7 (C), 170.3 (C), 157.3 (C), 142.1 (C), 135.6 (C), 129.3 (2 x CH), 128.2 (2 x CH), 126.2 (2 x CH), 125.8 (CH), 113.8 (2 x CH), 86.4 (C), 61.5 (CH_2), 58.0 (C), 55.4 (CH_3), 54.4 (CH_2), 53.6 (CH), 41.8 (CH_2), 36.4 (CH_2), 31.0 (CH_2), 23.4 (CH_2), 13.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{25}H_{30}NO_5$ $[M+H]^+$: 424.2119. found: 424.2129.

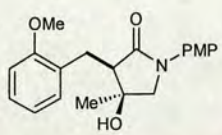


(±)-(3*R*,4*S*)-4-Hydroxy-1-(4-methoxyphenyl)-3,4-dimethylpyrrolidin-2-one (114a). The title compound was prepared according to General Procedure K from **113a** (47 mg, 0.20 mmol) for a reaction time of 2 h followed by Workup B and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (22 mg, 47%). m.p. 155-156 °C; IR ($CHCl_3$) 3410, 2934, 1675 (C=O), 1614, 1513, 1468, 1401, 1248, 1181,

1033 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49 (2H, dm, J = 9.0 Hz, Ar**H**), 6.88 (2H, dm, J = 9.0 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.78 (1H, d, J = 10.4 Hz, C**H**$_2$N), 3.69 (1H, d, J = 10.4 Hz, C**H**$_2$N), 2.51 (1H, q, J = 7.3 Hz, CH$_3$C**H**), 1.98 (1H, bs, O**H**), 1.47 (3H, s, C**H**$_3$COH), 1.24 (3H, d, J = 7.3 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.2 (C), 156.4 (C), 132.6 (C), 121.4 (2 x CH), 114.0 (2 x CH), 73.0 (C), 60.7 (CH_2), 55.4 (CH_3), 48.6 (CH), 24.7 (CH_3), 7.5 (CH_3); HRMS (FAB) Exact mass calcd for $C_{13}H_{18}NO_3$ $[M+H]^+$: 236.1282, found: 236.1293.

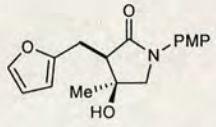


(±)-(3*R*,4*S*)-3-Benzyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (114c). The title compound was prepared according to General Procedure K from **113c** (62 mg, 0.20 mmol) for a reaction time of 4 h followed by Workup A and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (35 mg, 56%). Slow evaporation of a $CDCl_3$ solution of **109c** was found to give colourless crystals suitable for X-ray diffraction. m.p. 158-160 °C; IR ($CHCl_3$) 3346, 2928, 1661 (C=O), 1514, 1439, 1391, 1250, 1216, 1173, 1028 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.50 (2H, dm, J = 9.2 Hz, Ar**H**), 7.37-7.20 (5H, m, Ar**H**), 6.90 (2H, dm, J = 9.2 Hz, Ar**H**), 3.81 (3H, s, OC**H**$_3$), 3.70 (1H, d, J = 10.4 Hz, C**H**$_2$N), 3.60 (2H, d, J = 10.4 Hz, C**H**$_2$N), 3.37 (1H, dd, J = 14.3, 4.5 Hz, C**H**$_2$CH), 2.97 (1H, dd, J = 14.3, 9.7 Hz, C**H**$_2$CH), 2.81 (1H, dd, J = 9.7, 4.5 Hz, CH$_2$C**H**), 1.94 (1H, br s, O**H**), 1.14 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.2 (C), 156.5 (C), 140.1 (C), 132.4 (C), 129.1 (2 x CH), 128.5 (2 x CH), 126.3 (CH), 121.5 (2 x CH), 114.0 (2 x CH), 73.3 (C), 61.1 (CH_2), 55.4 (CH_3), 55.1 (CH), 30.8 (CH_2), 25.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{20}H_{22}NO_4$ $[M+H]^+$: 312.1594, found: 312.1594.

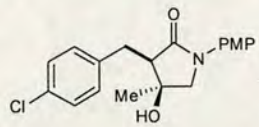


(±)-(3*R*,4*S*)-4-Hydroxy-3-(2-methoxybenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (132l). The title compound was prepared according to General Procedure L from **131l** (68 mg, 0.20 mmol) for a reaction time of 24 h followed by Workup B and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (50 mg, 74%). m.p. 136-137 °C; IR (film) 3451, 2935, 1687 (C=O), 1587, 1495, 1466, 1246, 1031, 829, 755, 733 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.51 (2H, dm,

J = 9.2 Hz, Ar**H**), 7.28-7.24 (1H, m, Ar**H**), 7.36 (1H, dd, J = 7.5, 1.7 Hz, Ar**H**), 6.99 (1H, td, J = 7.5, 1.1 H, Ar**H**), 6.94-6.91 (1H, m, Ar**H**), 6.90 (2H, dm, J = 9.2 Hz, Ar**H**), 3.92 (3H, s, OC**H**$_3$), 3.80 (3H, s, OC**H**$_3$), 3.65 (1H, br s, O**H**), 3.62 (2H, s, C**H**$_2$N), 3.24 (1H, dd, J = 14.3, 4.2 Hz, C**H**$_2$CH), 3.12 (1H, dd, J = 14.3, 11.2 Hz, C**H**$_2$CH), 2.75 (1H, dd, J = 11.2, 4.2 Hz, CH$_2$C**H**), 1.01 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.0 (C), 156.4 (2 x C), 132.5 (C), 131.0 (CH), 128.0 (C), 127.9 (CH), 121.9 (CH), 121.6 (2 x CH), 114.0 (2 x CH), 110.9 (CH), 72.6 (C), 60.4 (CH_2), 55.7 (CH_3), 55.4 (CH_3), 55.3 (CH), 26.0 (CH_3), 24.6 (CH_2); HRMS (FAB) Exact mass calcd for $C_{20}H_{24}NO_4$ $[M+H]^+$: 342.1700, found: 342.1700.

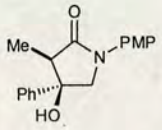


(3*R*,4*S*)-3-((furan-2-yl)methyl)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (132m). The title compound was prepared according to General Procedure K from **131m** (68 mg, 0.20 mmol) for a reaction time of 24 h followed by Workup B and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (33 mg, 55%). m.p. 155 °C; IR (film) 3419, 2925, 1675 (C=O), 1513, 1467, 1403, 1249, 1033, 933, 830 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 9.1 Hz, Ar**H**), 7.49 (1H, d, J = 1.3 Hz, Ar**H**), 6.89 (2H, d, J = 9.1 Hz, Ar**H**), 6.34 (1H, dd, J = 3.1, 2.0 Hz, Ar**H**), 6.17 (1H, d, J = 3.1 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.72 (1H, d, J = 10.4 Hz, C**H**$_2$N), 3.63 (1H, d, J = 10.4 Hz, C**H**$_2$N), 3.33 (1H, dd, J = 15.4, 4.3 Hz, ArC**H**$_2$), 3.05 (1H, dd, J = 15.4, 10.6 Hz, ArC**H**$_2$), 2.84 (1H, dd, J = 10.6, 4.3 Hz, ArCH$_2$C**H**), 2.28 (1H, s, O**H**), 1.19 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.5 (C), 156.5 (C), 153.2 (C), 141.0 (CH), 132.3 (C), 121.6 (2 x CH), 114.0 (2 x CH), 110.8 (CH), 106.8 (CH), 72.7 (C), 60.9 (CH_2), 55.8 (CH_3), 52.9 (CH), 25.7 (CH_3), 23.3 (CH_2)

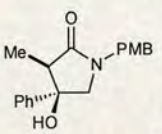


(±)-(3*R*,4*S*)-3-(4-chlorobenzyl)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (132n). The title compound was prepared according to General Procedure L from **131n** (69 mg, 0.20 mmol) for a reaction time of 24 h followed by Workup B and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (28 mg, 41%). m.p. 171 °C; IR (film) 3374, 2923, 1661 (C=O), 1512, 1368,

1247, 1170, 1028, 824 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49 (2H, dm, J = 9.1 Hz, Ar**H**), 7.36 (1H, d, J = 1.3 Hz, Ar**H**), 6.89 (2H, d, J = 9.1 Hz, Ar**H**), 6.34 (1H, dd, J = 3.1, 2.0 Hz, Ar**H**), 6.17 (1H, d, J = 3.1 Hz, Ar**H**), 3.80 (3H, s, OC**H**$_3$), 3.72 (1H, d, J = 10.4 Hz, C**H**$_2$N), 3.63 (1H, d, J = 10.4 Hz, C**H**$_2$N), 3.05 (1H, dd, J = 15.4, 10.6 Hz, ArC**H**$_2$), 2.84 (1H, dd, J = 10.6, 4.3 Hz, ArCH$_2$C**H**), 2.28 (1H, s, O**H**), 1.19 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.9 (C), 156.6 (C), 138.7 (C), 132.3 (CH), 132.0 (C), 130.5 (2 x CH), 128.6 (2 x CH), 121.6 (2 x CH), 114.1 (2 x CH), 73.3 (C), 61.2 (CH_2), 55.5 (CH), 55.1 (CH_3), 30.1 (CH_2), 25.8 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{20}ClNO_3$ $[M+H]^+$: 345.1700, found: 345.1701.



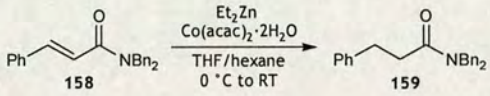
(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3-methyl-4-phenylpyrrolidin-2-one (134a). The title compound was prepared according to General Procedure M from **133a** (60 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (50% EtOAc/petrol) to give a white solid (34 mg, 57%). m.p. 123-125 °C; IR ($CHCl_3$) 3403 (OH), 2936, 1677 (C=O), 1511 (C=C), 1461, 1400, 1247, 1032, 829 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.57-7.55 (2H, m, Ar**H**), 7.51 (2H, dm, J = 9.2 Hz, Ar**H**), 7.46-7.41 (2H, m, Ar**H**), 7.38-7.33 (1H, m, Ar**H**), 6.89 (2H, dm, J = 9.2 Hz, Ar**H**), 4.06 (1H, d, J = 10.6 Hz, C**H**$_2$N), 3.87 (1H, d, J = 10.6 Hz, C**H**$_2$N), 3.79 (3H, s, OC**H**$_3$), 3.11 (1H, q, J = 7.2 Hz, CH$_3$C**H**), 2.50 (1H, s, O**H**), 1.22 (3H, d, J = 7.2 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.2 (C), 156.5 (C), 141.5 (C), 132.5 (C), 128.8 (2 x CH), 128.1 (CH), 125.2 (2 x CH), 121.4 (2 x CH), 114.1 (2 x CH), 77.2 (C), 61.6 (CH_2), 55.5 (CH_3), 48.5 (CH_2), 7.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1439.



(±)-(3*R*,4*R*)-4-Hydroxy-1-(4-methoxybenzyl)-3-methyl-4-phenylpyrrolidin-2-one (134b). The title compound was prepared according to General Procedure M from **133b** (62 mg, 0.20 mmol) for a reaction time of 8 h and purified by column chromatography (50% EtOAc/petrol) to give a white solid (33 mg, 53%). m.p. 133-135 °C; IR ($CHCl_3$) 3385 (OH), 2932, 1671 (C=O), 1512 (C=C), 1445, 1245, 1032, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.46-7.28 (5H, m, Ar**H**), 7.20 (2H, dm, J = 8.7 Hz, Ar**H**), 6.85 (2H, dm, J = 8.7

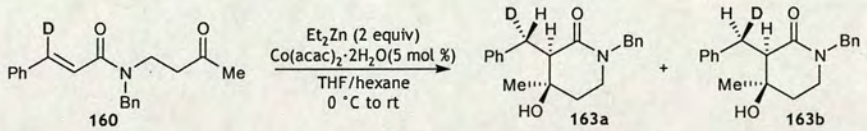
Hz, Ar**H**), 4.50 (2H, s, C**H**$_2$Ar), 3.76 (3H, s, OC**H**$_3$), 3.51 (1H, d, J = 10.8 Hz, HOCC**H**$_2$N), 3.35 (1H, d, J = 10.8 Hz, HOCC**H**$_2$N), 2.97 (1H, q, J = 7.2 Hz, CH$_3$C**H**), 2.10 (1H, br s, O**H**), 1.20 (3H, d, J = 7.2 Hz, C**H**$_3$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.1 (C), 159.1 (C), 141.9 (C), 129.4 (2 x CH), 128.6 (2 x CH), 128.2 (C), 127.9 (CH), 125.1 (2 x CH), 114.1 (2 x CH), 75.5 (C), 59.6 (CH_2), 55.2 (CH_3), 47.7 (CH), 45.9 (CH_2), 7.3 (CH_3); HRMS (FAB) Exact mass calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$: 312.1595, found: 312.1600.

Conjugate Reduction of α,β-Unsaturated Amide 158



A solution of the known cinnamic amide **158** (66 mg, 0.20 mmol) and $Co(acac)_2{\cdot}2H_2O$ (2.6 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature for 2h. The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/hexane) afforded the amide **159** (48 mg, 73%) that displayed identical spectroscopic data to those reported previously.

(±)-(3*R*,4*R*)-1-Benzyl-3-[(*RS*)-deuteriophenylmethyl]-4-hydroxy-4-methylpiperidin-2-one (163).



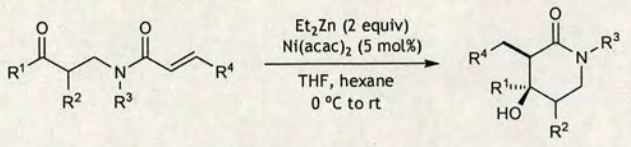
General Procedure K was followed using substrate **160** (62 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A to give **163** as a 2.6:1 inseparable mixture of diastereomers. Purification of the residue by column chromatography (70% EtOAc/petrol) gave **163** as a white solid (52 mg, 84%) as a 2.6:1 inseparable mixture of diastereomers. m.p. 114-116 °C; IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1451, 1269, 1146, 918, 732, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.41 (2H, m, Ar**H**), 7.39-7.29 (7H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.75 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 4.58 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 3.47 (1H, ddd, J = 12.2, 9.0, 5.6 Hz, CH_2C**H**$_2$N), 3.35 (0.7H, d, J = 5.3 Hz, C**H**D), 3.22 (0.3H, d, J = 5.4 Hz, C**H**D), 3.13 (1H, ddd, J = 12.2, 5.9, 5.1 Hz, CH_2C**H**$_2$N), 2.72 (1H, d, J = 5.4 Hz, C**H**CH=O), 1.92-1.80 (2H, m, C**H**$_2$$CH_2$N), 1.76 (1H, br s, O**H**), 1.31 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.1 (C), 141.9 (C), 137.1 (C), 129.2 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 126.0 (CH), 71.0 (C), 54.2 (CH), 50.4 (CH_2), 43.0 (CH_2), 35.2 (CH_2), 32.5 (**C**HD, t, J_D = 19.5 Hz), 28.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{23}DNO_2$ $[M+H]^+$: 311.1864, found: 311.1862.

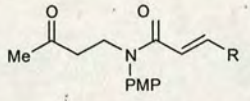
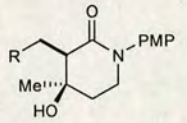
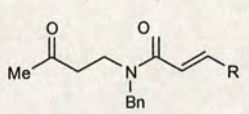
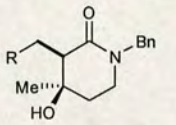
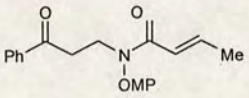
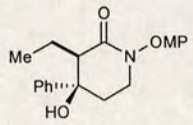
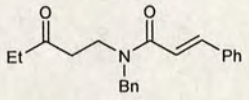
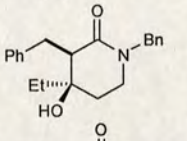
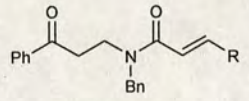
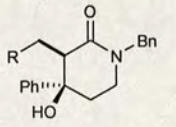
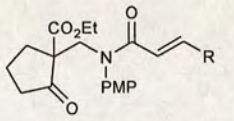
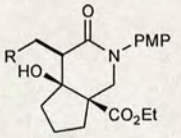
5. Nickel-Catalysed Reductive Aldol Cyclisations

The cobalt-mediated cyclisation of α,β-unsaturated carbonyl components tethered to a variety of ketones through an amide linkage allows the efficient synthesis of 4-hydroxypiperidine-2-ones and pyrrolidin-2-ones in moderate yields. Although the products were obtained with generally high levels of diastereoselectivity the process suffered from a number of limitations. Firstly, the substrate scope was limited to α,β-unsaturated amides as the corresponding esters proved to be unreactive under these conditions. Secondly, the process could not be rendered asymmetric through the use of chiral non-racemic ligands. Finally, the lack of literature president for cobalt-mediated coupling reactions in presence of diethylzinc reduced the possibilities of developing the reaction further. In order to overcome the limitations of the previously described cobalt-mediated methodology, our attention turned to the possibility of developing a nickel-catalysed reductive aldol reaction using diethylzinc as the stoichiometric reductant.

5.1. Results and Discussion[88]

Initial investigations into nickel-catalysed reductive aldol cyclisations began with reactions that provided six-membered β-hydroxylactams as products (Table 5.1). Using 5 mol% of $Ni(acac)_2$ in combination with two equivalents of Et_2Zn, a range of substrates underwent efficient cyclisation to give the corresponding 4-hydroxypiperidin-2-ones.



Entry	Substrate		Product		dr[a]	%Yield
1		R = Ph **89l**		**90l**	>19:1	62
2		R = 2-furyl **131a**		**132a**	>19:1	75
3		R = ^{i}Pr **131b**		**132b**	>19:1	70
4		R = Me **170a**		**171a**	>19:1	75
5		R = Me **170b**		**171b**	>19:1	97[b]
6		R = ^{i}Pr **131d**		**132d**	12:1	98[b]
7		R = CH_2CH_2Ph **171c**		**171c**	>19:1	95[b]
8		R = Ph **131e**		**132e**	>19:1	97[b]
9		R = 2-furyl **131f**		**132f**	>19:1	>99[b]
10		**89k**		**90k**	>19:1	62
11		**170d**		**171d**	>19:1	82[b]
12		R = Me **131g**		**132g**	9:1	84[b]
13		R = ^{t}Bu **131h**		**132h**	12:1	84[b]
14		R = 2-furyl **170e**		**171e**	>19:1	79[b]
15		R = Me **131j**		**132j**	>19:1	62[c]
16		R = Ph **131k**		**132k**	>19:1	50[c]

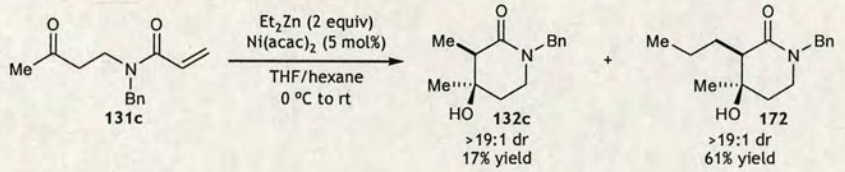
[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures; [b]Results taken from Pekka Joensuu; [c]Results taken from Euan Fordyce

Table 5.1

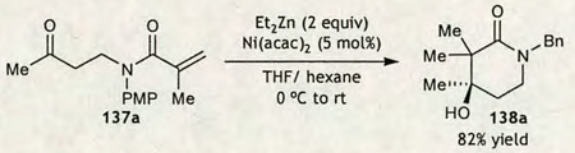
A variety of substituents at the α,β-unsaturated amide, including alkyl (entries 3-7, 10, 12, 13 and 15), aromatic (entries 1, 8 and 16) and heteroaromatic (entries 2, 9 and 14) groups were tolerated to give the corresponding cyclised products in good to excellent yields and with generally high diastereoselectivies. Furthermore, variations of the ketone component are accommodated, with alkyl (entries 1-9 and 11), cycloalkyl (entries 15 and 16) and aromatic (entries 10 and 12-14) ketones all proving effective acceptor electrophiles. A variety of nitrogen protecting groups can also be used, with benzyl (entries 5-9 and 11-14), *para*-methoxyphenyl (entries 1-4

and 15-16) and *ortho*-methylphenyl (entry 10) all being tolerated. In addition, the pre-existing stereocentre in substrates **131j** and **131k**, allows the cyclisation to occur with high levels of internal asymmetric induction to furnish the bicyclic 4-hydroxypiperidin-2-ones **132j** and **132k** respectively. Generally, the results presented for the nickel-catalysed reductive aldol cyclisation (Table 5.1) are comparable to those previously reported using $Co(acac)_2 \cdot 2H_2O$ as the precatalyst (Table 4.2).

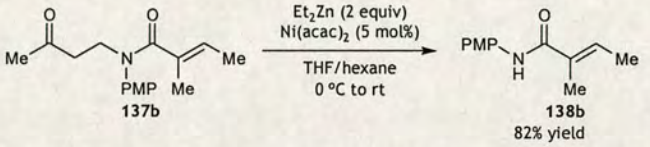
On the other hand simple acrylamides were observed to be less competent substrates under these conditions, due to their tendency to favour alkylative aldol cyclisation over reductive aldol cyclisation. For example, acrylamide **131c** provided the desired reductive aldol product **132c** in only 17% yield, with the major product **172** occurring due to the conjugate addition of an ethyl group followed by cyclisation (eq 44). Conversely, when $Co(acac)_2 \cdot 2H_2O$ is used as the precatalyst in place of $Ni(acac)_2$ the desired reductive aldol product **132c** is obtained in 88% yield with no formation of the alkylated product **172** being detected. Substitution at the α-position of the acrylamide allowed the reductive aldol cyclisation to re-establish itself as the dominant reaction pathway. This was illustrated by the efficient cyclisation of the methacrylamide substrate **137a** to provide lactam **138a** containing two contiguous quaternary centres in 82% yield (eq 45). Subsequent extension of this methodology to the reductive aldol cyclisation of trisubstituted α,β-unsaturated amides has met with only limited success. Tiglic acid derivate **137b** did not undergo cyclisation, providing the elimination product **138b** instead (eq 46). However, α,β-unsaturated amide **173** provided the desired lactam product **174** in moderate yield (eq 47). Most notably attempted cyclisations of substrates **137a,b** and **173** using $Co(acac)_2 \cdot 2H_2O$ as the precatalyst failed.



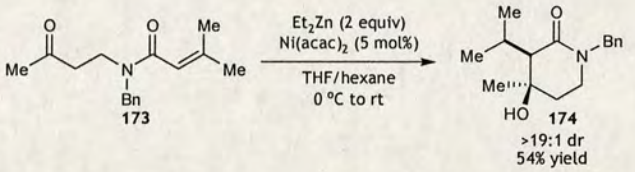
(44)



(45)

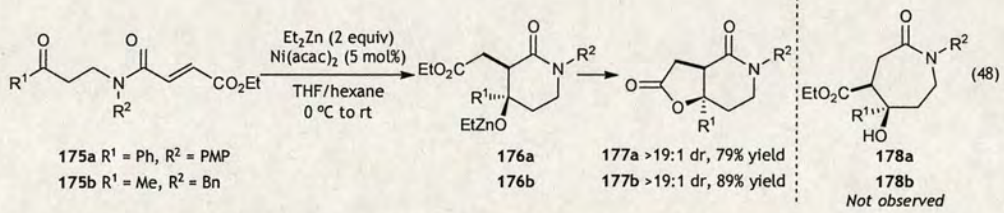


(46)



(47)

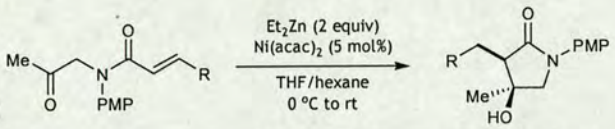
Substrates **175a** and **175b** incorporating a pendant ester group on the α,β-unsaturated amide component, cyclised efficiently affording bicyclic products **177a** and **177b** respectively. Seemingly this occurs as a consequence of the tertiary zinc alkoxides **176a** and **176b**, produced from the initial reductive cyclisation, undergoing lactonisation with the pendant ester groups (eq 48; results from Pekka Joensuu).



(48)

Remarkably, alternative regioisomeric products **178a** and **178b**, resulting from cyclisation α- to the ester as apposed to the amide were not detected in the product mixtures. This effectively demonstrates the high levels of chemoselectivity that are attainable via this methodology. Equally, attempted cyclisations of **175a** and **175b** using $Co(acac)_2 \cdot 2H_2O$ in place of $Ni(acac)_2$ failed to give any product.

The application of this methodology to the synthesis of pyrrolidin-2-ones proved moderately successful (Table 5.2). Substrates with a diverse array of substitution at the β-position of the α,β-unsaturated amide component, including alkyl (entries 1 and 2), aromatic (entries 4 and 5) and ester groups (entry 3) undergo efficient cyclisation. In comparison to the cyclisation of substrates **175a** and **175b** (eq 48), the cyclisation of **179c** resulted in <10% lactonisation.



Entry	R	Product	dr[a]	%Yield
1	R = Me **179a**	**180a**	5:1	42
2	R = ^{i}Pr **179b**	**180b**	5:1	70
3	R = CO_2Et **179c**	**180c**	>19:1	76[b]
4	R = 2-MeOPh **131l**	**132l**	>19:1	58
5	R = 2-furyl **131m**	**132m**	>19:1	32
6	R = Ph **113c**	**114c**	>19:1	23
7	R = 4-ClPh **131n**	**132n**	-	<5

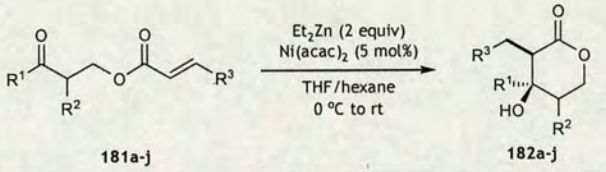
[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures
[b]Results taken from Pekka Joensuu

Table 5.2

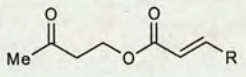
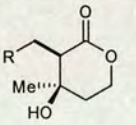
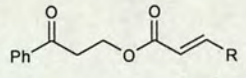
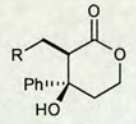
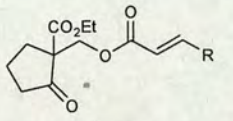
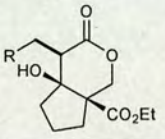
Although these results are comparable to those obtained when $Co(acac)_2 \cdot 2H_2O$ is used as the precatalyst (Table 4.2), a number of subtle differences are worthy of note. Firstly, substrates containing electron-deficient groups such as **131n** (entry 7) are not competent substrates under the nickel-catalysed conditions. However, under the cobalt-catalysed conditions, substrate **131n** underwent cyclisation to give the corresponding pyrrolidin-2-one **132n** in 41% yield with a diastereomeric ratio of 5:1 (Table 4.2, entry 18). Consequently, by increasing the electron-donating ability of the pendant aromatic group the products can be obtained in enhanced yields (entries 4, 5 and 6). Even so, under the cobalt-catalysed conditions the corresponding cyclisations react with greater efficiency and with generally superior yields (Table 4.2, entries 14-18). Secondly, substrates containing alkyl or ester substituted α,β-unsaturated amide components **179a**, **179b** and **179c** cyclise more readily under the nickel-catalysed methodology, giving the corresponding products in moderate to good yields (entries

1, 2 and 3). In contrast, substrates **179a**, **179b** and **179c** react poorly under the cobalt-catalysed conditions (Chapter 4).

The synthetic utility of this methodology was further enhanced by the application to the cyclisation of oxygen-linked substrates. In contrast to the use of $Co(acac)_2 \cdot 2H_2O$ as the pre-catalyst, where productive cyclisations could not be achieved for ester-linked precursors, the combination of $Ni(acac)_2/Et_2Zn$ was found to give efficient cyclisations to furnish a range of β-hydroxylactones in high yield and with high diastereoselectivities (Table 5.3; results taken from Pekka Joensuu).



181a-j **182a-j**

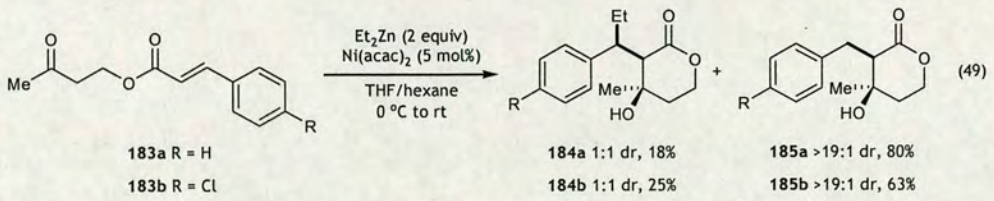
Entry	Substrate		Product		dr[a]	%Yield
1		R = ^{t}Bu **181a**		**182a**	>19:1	77
2		R = CH_2CH_2Ph **181b**		**182b**	>19:1	85
3		R = 4-MeOPh **181c**		**182c**	>19:1	76
4		R = 2-furyl **181d**		**182d**	>19:1	81
5		R = ^{t}Bu **181e**		**182e**	5.5:1	99
6		R = CH_2CH_2Ph **181f**		**182f**	>10:1	76
7		R = 2-furyl **181g**		**182g**	n.d.	75
8		R = Me **181h**		**182h**	>19:1	88
9		R = ^{i}Pr **181i**		**182i**	>19:1	74
10		R = Ph **181j**		**182j**	>19:1	73

[a]Determined by ^1H NMR analysis of the unpurified reaction mixtures

Table 5.3

Subtle electronic effects were revealed in the cyclisation of oxygen-linked cinnamic substrates. The cyclisation of the 4-methoxy-substituted precursor **181c** gave only the expected reductive aldol product in 76% yield (Table 5.3, entry 3), whereas substrates incorporating less electron-rich substituents provided significant quantities of alkylative aldol products **184a** and **184b** respectively as inseparable 1:1 mixtures of diastereomers (eq 49; results taken from Pekka Joensuu). From these results it

would appear that as the aromatic substituent becomes more electron-withdrawing, the extent of alkylative aldol cyclisation becomes more prevalent.



183a R = H
183b R = Cl

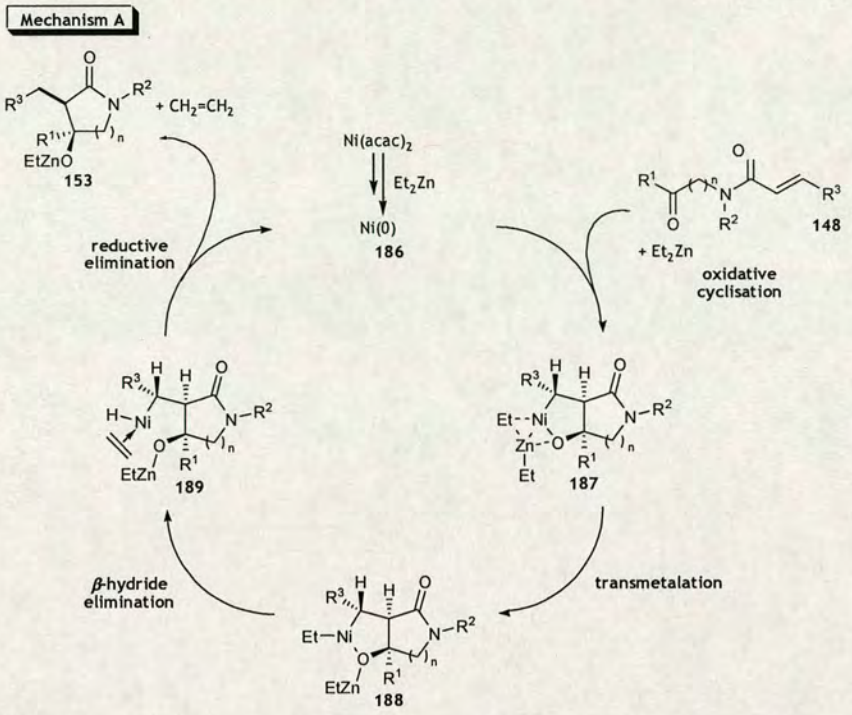
184a 1:1 dr, 18%
184b 1:1 dr, 25%

185a >19:1 dr, 80%
185b >19:1 dr, 63%

5.1.1. Proposed Mechanism

As previously illustrated (Chapter 2) there are a number of mechanistic possibilities that have been proposed to account for the observed products in nickel-catalysed reductive couplings and cyclisations. It is generally accepted that the treatment of $Ni(acac)_2$ with Et_2Zn results in the reduction of Ni(II) to Ni(0) and we believe that the same process is operative in our methodology. From the mechanistic possibilities proposed for nickel-catalysed reductive couplings and cyclisations, two appeared applicable to our methodology.

Firstly, the involvement of metallacyclic intermediates has been proposed for a large number of nickel-catalysed reductive couplings and cyclisations. The formation of metallacyclic intermediates has been attributed to the oxidative cyclisation of Ni(0) with two π-components. Through the analysis of oxidative cyclisation products by X-ray crystallography, the participation of metallacyclic intermediates could be inferred.[48,89] Although our nickel-catalysed methodology is formally a reductive aldol process, it is possible that the mechanistic pathway involves a metallacyclic intermediate as illustrated (Scheme 5.1).

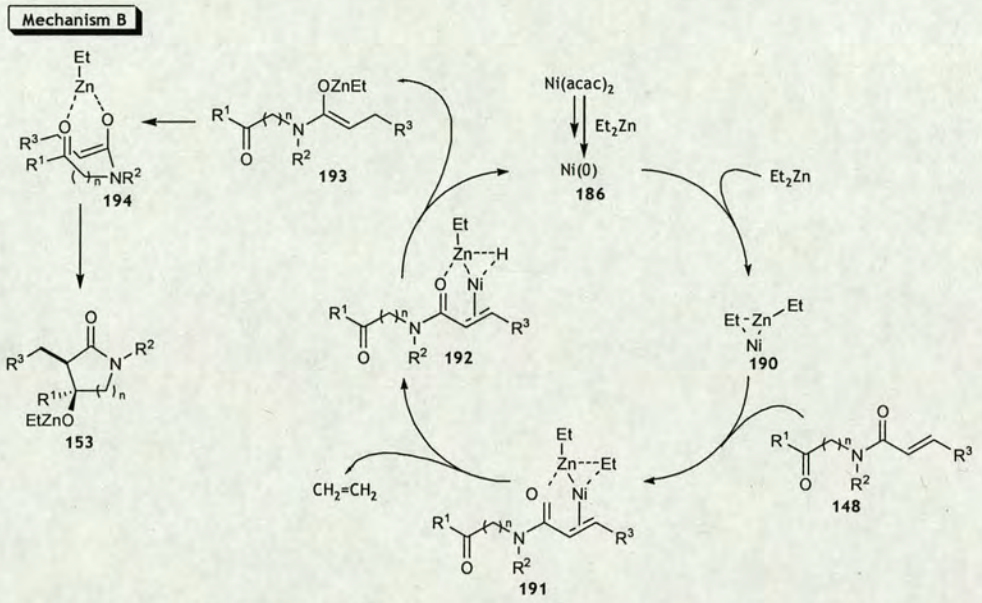


Scheme 5.1

This mechanism is analogous to that previously described for the cobalt-catalysed reductive aldol cyclisation (Chapter 4; Scheme 4.2). In the case of nickel-catalysis detailed studies conducted by Montgomery and co-workers[38] suggest that diethylzinc facilitates the oxidative cyclisation through initial Lewis acid activation of the ketone by co-ordination with zinc, followed by subsequent Lewis base activation of Ni(0) through a three-centre-two-electron bridging of a zinc-ethyl bond. This type of Lewis acid promoted rate acceleration has been previously reported for a variety of nickel-catalysed oxidative cyclisations.[89c,d] As observed under our cobalt-catalysed methodology, the relative stereochemistry of the cyclised products is related to the formation of the bicyclic intermediate preferring to adopt an energetically more favourable *cis*-ring junction as opposed to the higher energy *trans*-ring junction.

In addition, a second plausible mechanism which involves the intervention of discrete enolate intermediates (Scheme 5.2), is also analogous to that previously

described for the cobalt-catalysed reductive aldol cyclisation (Chapter 4; Scheme 4.1).

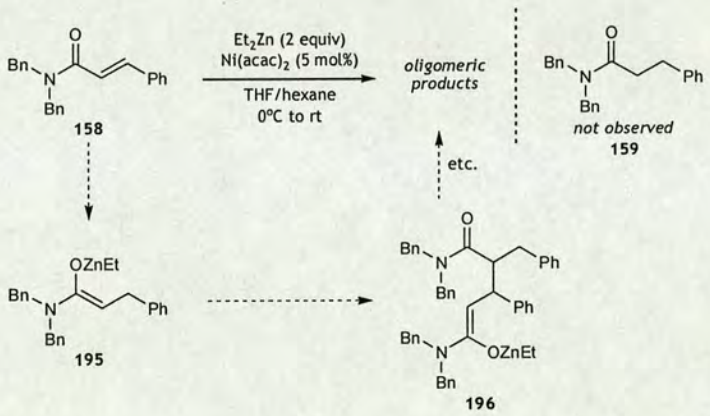


Scheme 5.2

If mechanism B (Scheme 5.2) is the dominant process then one could suggest that the proportion of alkylative aldol cyclisation products from precursors **183a** and **183b** (eq 49), is dependant on the particular steric/electronic properties of the substrate enabling conjugate addition from **191** to compete with β-hydride elimination to **192**. On the other hand the formation of **184a** and **184b** can be rationalised by invoking mechanism A (Scheme 5.1) if reductive elimination from **188** competes with β-hydride elimination to **189**. However, the isolation of products **184a** and **184b** as a 1:1 mixture of diastereomers cannot be explained using mechanism A, assuming all steps in mechanism A are stereospecific.

Furthermore, we examined the reaction of α,β-unsaturated amide **158** in the absence of the pendant ketone π-system to our standard conditions (Scheme 5.3; results taken from Pekka Joensuu) in an effort to identify which mechanism is in operation. Principally, mechanism B (Scheme 5.2) does not require the presence of a second

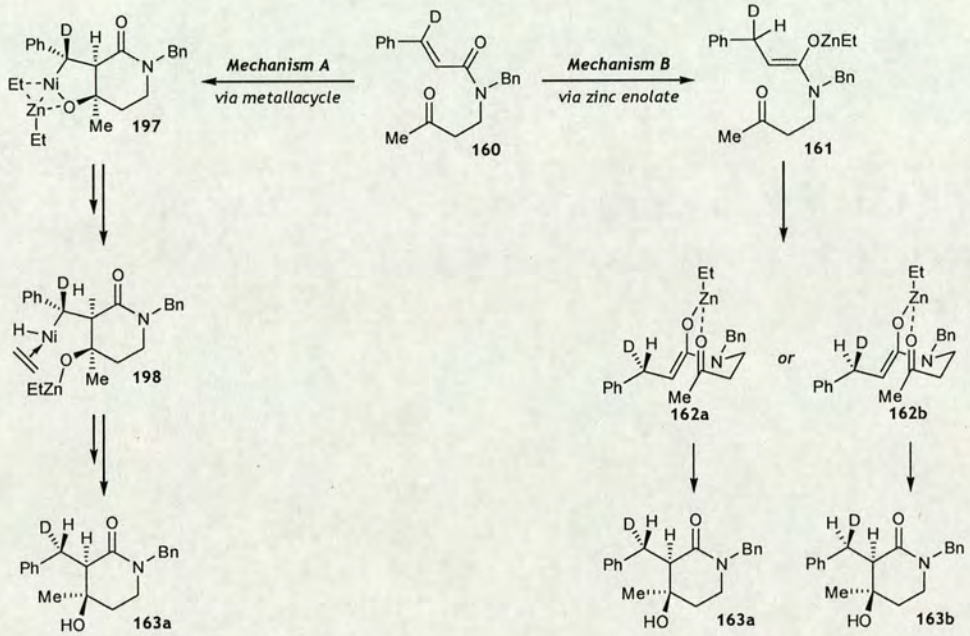
electrophilic π-component until after the zinc enolate is formed; however, in mechanism A the ketone π-component is an essential prerequisite for oxidative cyclisation to form the proposed oxanickellacycle (Scheme 5.1). Consequently, if mechanism B is in operation one would expect to observe the product of conjugate reduction **159**. In the event, exposure of **158** to our standard conditions provided only a complex mixture of products which appeared to be composed of oligomeric products, with none of the desired amide **159** being observed. The failure to detect **159** does not exclude mechanism B as a possibility, since the zinc enolate **195** that would be formed from conjugate addition of **158** could react with another molecule of **158** in a Michael addition, generating another zinc enolate **196** which could then participate in further reactions resulting in oligomeric products. This type of behaviour has been previously noted for poorly chemoselective 1,4-addition reactions of organometallic reagents. The outcome of this reaction differs from that previously obtained using $Co(acac)_2 \cdot 2H_2O$ in place of $Ni(acac)_2$, where amide **159** was formed in 73% yield (Chapter 4; eq 42).



Scheme 5.3

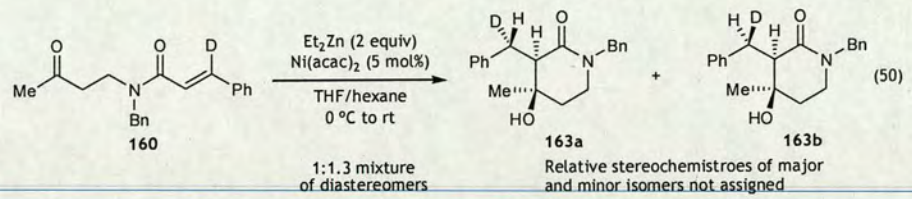
As in (Chapter 4; eq 43) we next conducted the cyclisation of deuterium labelled substrate **160** (Scheme 5.4). If mechanism A is operative, the concerted nature of the oxidative cyclisation would be expected to provide metallacycle **197** with the relative stereochemistry shown. An eventual reductive elimination of nickel hydride **198** that proceeds with retention of configuration would be expected to produce a single

diastereomer of cyclised product **163a**. However, if mechanism B is operative *via* the proposed zinc enolate **161**, we should expect to observe the cyclised product as a *ca.* 1:1 mixture of diastereomers **163a** and **163b**, due to the diastereomeric Zimmerman-Traxler-type transition states[13] **162a** and **162b** possessing near identical energies.



Scheme 5.4

In the event, the nickel-catalysed reductive cyclisation of **160** afforded a 1:1.3 inseparable mixtures of diastereomers **163a** and **163b** as determined of NMR spectroscopy of the unpurified reaction mixture (eq 50; results taken from Pekka Joensuu).



As a result several possible explanations could be used to rationalise the observed diastereomeric ratio. Firstly, both mechanism A and B are operative as competing

reaction pathways. Secondly, mechanism A is operative, but one or more steps in the pathway are not stereospecific. This may in part be due to the conformational lability of a carbon–nickel bond allowing epimerisation. Thirdly, if mechanism B is operative, initial precoordination of either nickel or zinc with both carbonyl groups could facilitate a degree of facial selectivity during the reduction of the α,β-unsaturated system. This is probable as the chelate effect will favour the substrate acting as a bidenate ligand and the coordination of oxygen will activate the α,β-unsaturated system to reduction. Even so it is possible that mechanism A and B are over simplifications of a more complex mechanistic system. Although on the available evidence, mechanism A cannot be completely discounted at this stage, we presently favour a variation of mechanism B as the probable reaction pathway based on the results from the deuterium-labelling studies. Further aspects of the mechanism not discussed within the context of mechanism B which could be responsible for a non-equimolar distribution of diastereomers **163a/163b** include the conformation/hapticity of zinc enolate intermediates (oxa-π-allyl species, *C*-bound versus *O*-bound enolates) and fluctuations in the hapticity in the course of the reaction. A definitive determination of the reaction mechanism will therefore require additional studies.

On comparison with the results obtained using $Co(acac)_2 \cdot 2H_2O$ as the precatalyst (eq 43), the degree of diastereoselection was increased, and most interestingly the sense of diastereoselection was reversed (eq 50). In general the disparity between the cobalt-catalysed and the nickel-catalysed methodology is demonstrated through the broader substrate scope of the nickel system and their divergent behaviour with simple acrylamides **137a** and with substrates lacking a pendant ketone **158**, the end result of this isotopic labelling study also indicates variations in their mechanisms.

5.2. Conclusions and Future Work

It has been demonstrated that in the presence of diethylzinc, $Ni(acac)_2$ acts as an effective pre-catalyst in the reductive aldol cyclisation of substrates containing α,β-unsaturated carbonyl moieties tethered to a variety of ketones through either an

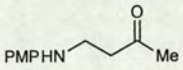
amide or an ester linkage. In these reactions diethylzinc serves as a stoichiometric reducing agent, delivering a hydride to the β-position of the α,β-unsaturated carbonyl component, leading to the formation of several β-hydroxylactams and β-hydroxylactones with generally high levels of diastereoselection. Comparison with the previously discussed cobalt-catalysed methodology demonstrates that the nickel-catalysed methodology is superior in both substrate scope and general reactivity. Through the use of deuterium labeling studies, the disparity between the cobalt- and nickel-catalysted methodology was further re-enforced indicating that both processes proceed through different complex mechanisms.

5.3. Experimental

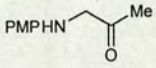
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontour.com 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. Non-commercially available α,β-unsaturated carboxylic acids used in the preparation of the cyclization substrates were obtained as follows: (*E*)-5-methylhex-2-enoic acid was prepared from a Wadsworth-Emmons reaction of isovaleraldehyde with triethyl phosphonoacetate, followed by hydrolysis of the resulting ethyl ester, according to literature procedures; (*E*)-5-phenylpent-2-enoic acid was prepared analogously using hydrocinnamaldehyde (distilled before use) in place of isovaleraldehyde. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[80] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan

MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound.

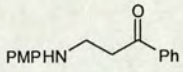
Preparation of Aminoketones



4-(4-Methoxyphenylamino)butan-2-one (118). Prepared according to a previously reported procedure (Chapter 3.3).

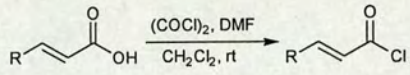


1-(4-Methoxyphenyl)aminopropanone (126). Prepared according to a previously reported procedure (Chapter 3.3)

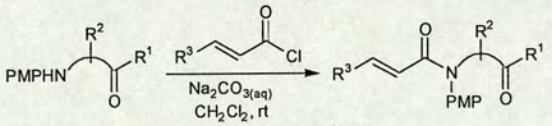


3-(4-Methoxyphenylamino)-1-phenylpropan-1-one(121). Prepared according to a previously reported procedure (Chapter 3.3)

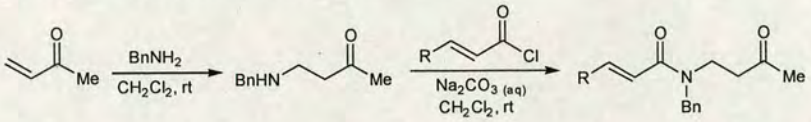
Preparation of α,β-Unsaturated Acid Chlorides: Prepared according to the previously described **General Procedure H**.



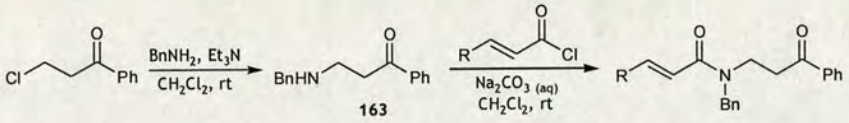
Preparation of Amide-Tethered Cyclization Precursors: Prepared according to the previously described **General Procedure D**.

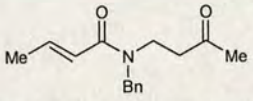


Preparation of Amide-Tethered Cyclization Precursors: Prepared according to the previously described **General Procedure I.**

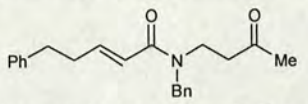


Preparation of Amide-Tethered Cyclization Precursors: Prepared according to the previously described **General Procedure K**.

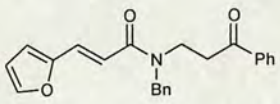




***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-but-2-enamide (170b).** The title compound was prepared according to General Procedure I from methyl vinyl ketone (0.94 mL, 11.0 mmol), benzylamine (1.09 mL, 10.0 mmol), and crotonoyl chloride (1.29 mL, 12.1 mmol) for a reaction time of 4 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a colourless oil as a 2:1 mixture of rotamers. IR (film) 2914, 1713 (C=O), 1660 (C=C), 1449, 1369, 1160, 963, 815, 732, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.36-7.25 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 7.07-6.91 (1H, m, $CH_3C\mathbf{H}$=), 6.20 (1H, dq, J = 14.9, 1.5 Hz, C**H**C=O), 4.64 (2H, s, C$\mathbf{H_2}$Ph), 3.59 (2H, t, J = 6.7 Hz, $CH_2C\mathbf{H_2}N$), 2.79 (2H, t, J = 6.7 Hz, C$\mathbf{H_2}CH_2N$), 2.10 (3H, s, C$\mathbf{H_3}$C=O), 1.82 (3H, dd, J = 6.9, 1.5 Hz, C$\mathbf{H_3}$CH=); (Minor rotamer) δ 7.36-7.25 (4H, m, Ar**H**), 7.17-7.15 (1H, m, Ar**H**), 7.07-6.91 (1H, m, $CH_3C\mathbf{H}$=), 6.29 (1H, d, J = 14.9 Hz, C**H**C=O), 4.64 (2H, s, C$\mathbf{H_2}$Ph), 3.59 (2H, t, J = 7.2 Hz, $CH_2C\mathbf{H_2}N$), 2.63 (2H, t, J = 7.2 Hz, C$\mathbf{H_2}CH_2N$), 2.07 (3H, s, C$\mathbf{H_3}$C=O), 1.90 (3H, d, J = 6.5 Hz, C$\mathbf{H_3}$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.0 (C), 205.7 (C), 166.7 (C), 166.1 (C), 142.2 (CH), 141.9 (CH), 137.4 (C), 136.8 (C), 128.4 (CH), 128.1 (CH), 127.6 (CH), 127.1 (CH), 126.9 (CH), 126.0 (CH), 121.3 (CH), 121.0 (CH), 51.6 (CH_2), 48.8 (CH_2), 42.4 (CH_2), 41.8 (CH_2), 41.4 (CH_2), 29.8 (CH_3), 29.6 (CH_3), 17.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{19}NO_2$ $[M+H]^+$: 246.1489, found: 246.1489.

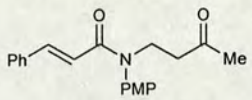


***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-5-phenylpent-2-enamide (170c)**. The title compound was prepared according to General Procedure I from methyl vinyl ketone (0.56 mL, 6.60 mmol), benzylamine (0.65 mL, 6.00 mmol), and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-phenylpent-2-enoic acid (1.34 g, 7.26 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give a pale yellow oil (1.27 g, 63%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2924, 1712 (C=O), 1657 (C=C), 1495, 1425, 1390, 1206, 970, 735, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.37-7.13 (10H, m, Ar**H**), 7.10-6.94 (1H, m, =C**H**), 6.18 (1H, d, J = 15.1 Hz, =C**H**), 4.59 (2H, s, NC$\mathbf{H}_2$Ph), 3.60 (2H, t, J = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.84-2.46 (6H, m, $C\mathbf{H}_2CH_2N$ and $PhC\mathbf{H}_2C\mathbf{H}_2$), 2.12 (3H, s, $C\mathbf{H}_3C$=O); (Minor rotamer) 7.37-7.13 (10H, m, Ar**H**), 7.10-6.94 (1H, m, =C**H**), 6.23 (1H, d, J = 17.1 Hz, =C**H**), 4.63 (2H, s, NC$\mathbf{H}_2$Ph), 3.53 (2H, t, J = 7.2 Hz, C$\mathbf{H}_2$N), 2.84-2.46 (6H, m, $C\mathbf{H}_2CH_2N$ and $PhC\mathbf{H}_2C\mathbf{H}_2$), 2.06 (3H, s, $C\mathbf{H}_3C$=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.4 (C), 206.1 (C), 167.1 (C), 166.4 (C), 146.2 (CH), 145.7 (CH), 140.8 (C), 137.6 (C), 137.1 (C), 128.8 (CH), 128.5 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 126.0 (CH), 120.9 (CH), 120.5 (CH), 52.1 (CH_2), 49.3 (CH_2), 42.7 (CH_2), 42.2 (CH_2), 41.8 (CH_2), 41.7 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 30.2 (CH_3), 30.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1958, found: 336.1959.

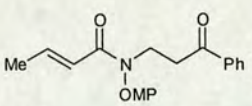


***N*-Benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-3-furan-2-ylpropenamide (170e)**. The title compound was prepared according to General Procedure K from 3-chloropropiophenone (1.85 g, 11.0 mmol), benzylamine (1.10 mL, 10.0 mmol) and 3-(2-furyl)acrylic acid (2.07 g, 15.0 mmol) for a reaction time of 5 h. The product was purified by column chromatography (15% EtOAc/$CHCl_3$) to give an orange gum (2.26 g, 63%) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2942, 1682 (C=O), 1651 (C=C), 1487, 1324, 1213, 971, 733, 692, 594 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 8.01 (2H, d, J = 7.7 Hz, Ar**H**), 7.61-7.28 (9H, m, Ar**H**), 7.58 (1H, d, J = 15.1 Hz, =C**H**), 6.82 (1H, d, J = 15.1 Hz, =C**H**), 6.58 (1H, d, J = 3.3 Hz, C**H**)

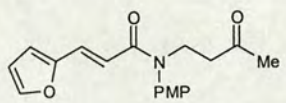
6.46-6.45 (1H, m, C**H**), 4.84 (2H, s, NC**H**$_2$Ph), 3.88 (2H, t, J = 6.8 Hz, C**H**$_2$N), 3.43 (2H, t, J = 6.8 Hz, C**H**$_2$CH$_2$N); (Minor rotamer) δ 7.90 (2H, d, J = 7.6 Hz, Ar**H**), 7.64 (1H, d, J = 15.0 Hz, =C**H**), 7.61-7.28 (9H, m, Ar**H**), 6.91 (1H, d, J = 15.0 Hz, =C**H**), 6.61 (1H, d, J = 3.2 Hz, C**H**) 6.49-6.48 (1H, m, C**H**), 4.81 (2H, s, NC**H**$_2$Ph), 3.92 (2H, t, J = 7.4 Hz, C**H**$_2$N), 3.27 (2H, t, J = 7.4 Hz, C**H**$_2$CH$_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 198.7 (C), 197.5 (C), 166.9 (C), 166.2 (C), 151.3 (C), 143.8 (CH), 137.5 (C), 137.0 (C), 136.4 (C), 136.1 (C), 133.3 (CH), 133.0 (CH), 130.2 (CH), 129.7 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.8 (CH), 127.4 (CH), 127.2 (CH), 126.4 (CH), 114.6 (CH), 114.2 (CH), 114.0 (CH), 113.9 (CH), 112.0 (CH), 52.2 (CH_2), 49.4 (CH_2), 43.2 (CH_2), 42.5 (CH_2), 38.1 (CH_2), 37.0 (CH_2); HRMS (ES) Exact mass calcd for $C_{23}H_{22}NO_3$ $[M+H]^+$: 360.1594, found: 360.1590.



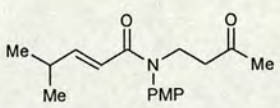
***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenoate (89l)**. Prepared according to a previously reported procedure (Chapter 3.3).



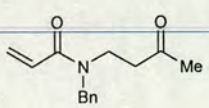
***N*-(2-Methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)-(*E*)-but-2-enamide (89k)**. Prepared according to a previously reported procedure (Chapter 3.3).



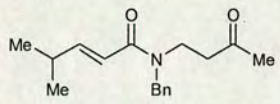
***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (131a)**. Prepared according to a previously reported procedure (Chapter 4.3).



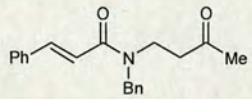
***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-4-methylpent-2-enamide (131b)**. Prepared according to a previously reported procedure (Chapter 4.3).



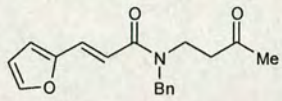
***N*-Benzyl-*N*-(3-oxobutyl)propenamide (131c)**. Prepared according to a previously reported procedure (Chapter 4.3).



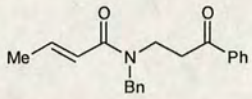
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-4-methylpent-2-enamide (131d)**. Prepared according to a previously reported procedure (Chapter 4.3).



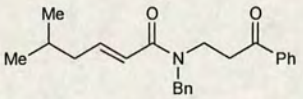
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-phenylpropenamide (131e)**. Prepared according to a previously reported procedure (Chpater 4.3)



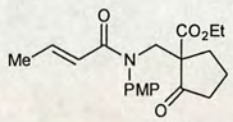
***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-furan-2-ylpropenamide (131f)**. Prepared according to a previously reported procedure (Chapter 4.3).



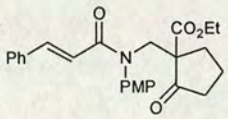
***N*-Benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-but-2-enamide (131g)**. Prepared according to a previously reported procedure (Chapter 4.3).



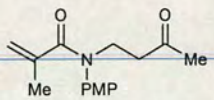
***N*-benzyl-*N*-(3-oxo-3-phenylpropyl)-(*E*)-5-methylhex-2-enamide (131h)**. Prepared according to a previously reported procedure (Chapter 4.3).



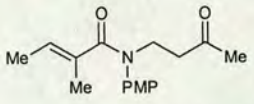
1-[*N*-(*E*)-But-2-enoyl-*N*-(4-methoxyphenyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (131j). Prepared according to a previously reported procedure (Chapter 4.3).



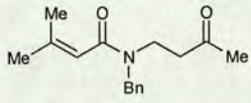
1-[*N*-(4-Methoxyphenyl)-*N*-((*E*)-3-phenylacryloyl)aminomethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (131k). Prepared according to a previously reported procedure (Chapter 4.3).



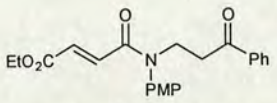
***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-2-methylpropenamide (137a)**. Prepared according to a previously reported procedure (Chapter 4.3).



***N*-(4-Methoxyphenyl)-*N*-(3-oxobutyl)-(*E*)-2-methylbut-2-enamide (137b)**. Prepared according to a previously reported procedure (Chapter 4.3).

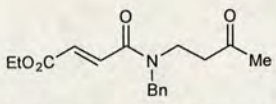


***N*-Benzyl-*N*-(3-oxobutyl)-3-methylbut-2-enamide (173)**. The title compound was prepared according to General Procedure I from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according General Procedure A) derived from 3,3-dimethylacrylic acid (2.87 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give yellow oil (2.72 g, 52%) as a 2:1 mixture of rotamers. IR (film) 2912, 1714 (C=O), 1620 (C=C), 1452, 1371, 1163, 942, 846, 735, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.34-7.14 (5H, m, Ar**H**), 5.83 (1H, s, =C**H**), 4.58 (2H, s, C**H**$_2$Ph), 3.54 (2H, t, J = 6.8 Hz, C**H**$_2$N), 2.75 (2H, t, J = 6.8 Hz, C**H**$_2$CH$_2$N), 2.09 (3H, s, C**H**$_3$C=O), 1.96 (3H, s, (C**H**$_3$)$_2$C), 1.78 (3H, s, (C**H**$_3$)$_2$C); (Minor rotamer) δ 7.34-7.14 (5H, m, Ar**H**), 5.91 (1H, s, =C**H**), 4.60 (2H, s, C**H**$_2$Ph), 3.54 (2H, t, J = 7.2 Hz, C**H**$_2$N), 2.59 (2H, t, J = 7.2 Hz, C**H**$_2$CH$_2$N), 2.03 (3H, s, C**H**$_3$C=O), 1.99 (3H, s, (C**H**$_3$)$_2$C), 1.85 (3H, s, (C**H**$_3$)$_2$C); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.2 (C), 206.0 (C), 168.6 (C), 168.0 (C), 147.8 (C), 137.6 (C), 137.0 (C), 128.6 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 127.1 (CH), 126.5 (CH), 117.5 (CH), 117.2 (CH), 52.3 (CH_2), 48.0 (CH_2), 42.2 (CH_2), 42.0 (CH_2), 41.6 (CH_2), 40.9 (CH_2), 30.0 (CH_3), 29.8 (CH_3), 26.3 (CH_3), 26.1 (CH_3), 20.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_2$ $[M+H]^+$: 260.1645, found: 260.1644.



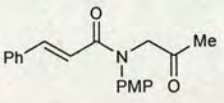
Ethyl (*E*)-3-[*N*-(4-methoxyphenyl)-*N*-(3-oxo-3-phenylpropyl)carbamoyl]acrylate (175a). The title compound was prepared according to General Procedure D from the amine **121** (663 mg, 2.60 mmol) and the acid chloride (prepared according to General Procedure A) derived from mono-ethyl fumarate (562 mg, 3.90 mmol) for a reaction time of 6 h and purified by column chromatography (30% EtOAc/petrol→50% EtOAc/petrol) to give a yellow/brown oil that solidified upon standing to a yellow solid (841 mg,

85%). m.p. 58-59 °C; IR ($CHCl_3$) 2981, 1717 (C=O), 1682 (C=O), 1630 (C=C), 1510, 1161, 1030, 840, 742, 691 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.89 (2H, d, J = 7.9 Hz, Ar**H**), 7.52-7.48 (1H, m, Ar**H**), 7.41-7.37 (2H, m, Ar**H**), 7.06 (2H, d, J = 8.4 Hz, Ar**H**), 6.88 (2H, d, J = 8.4 Hz, Ar**H**), 6.80-6.79 (2H, m, C**H**=C**H**), 4.19-4.09 (4H, m, OC$\mathbf{H}_2$ and C$\mathbf{H}_2$N), 3.77 (3H, s, OC$\mathbf{H}_3$), 3.30 (2H, t, J = 7.4 Hz, C$\mathbf{H}_2$CH$_2$N), 1.20 (3H, t, J = 7.1 Hz, OCH$_2$C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.9 (C), 165.4 (C), 164.2 (C), 159.2 (C), 136.4 (C), 134.1 (CH), 133.5 (C), 133.1 (CH), 130.9 (CH), 128.8 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 114.9 (2 x CH), 60.8 (CH_2), 55.3 (CH_3), 46.2 (CH_2), 36.2 (CH_2), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{24}NO_5$ $[M+H]^+$: 382.1649, found: 382.1648.

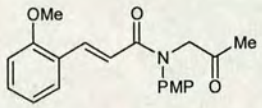


Ethyl (*E*)-3-[*N*-benzyl-*N*-(3-oxobutyl)carbamoyl]acrylate (175b). The title compound was prepared according to General Procedure I from methyl vinyl ketone (1.88 mL, 22.0 mmol), benzylamine (2.18 mL, 20.0 mmol) and the acid chloride (prepared according to General Procedure A) derived from mono-ethyl fumarate (3.93 g, 24.2 mmol) for a reaction time of 16 h. The product was purified by column chromatography (40% EtOAc/petrol) to give light yellow solid (2.51g, 55 %) as a 2:1 mixture of rotamers. IR ($CHCl_3$) 2983, 1716 (C=O), 1651 (C=O), 1625 (C=C), 1447, 1297, 1163, 1031, 973, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.37-7.15 (6H, m, Ar**H** and =C**H**), 6.84 (1H, d, J = 15.3 Hz, =C**H**), 4.68 (2H, s, C$\mathbf{H}_2$Ph), 4.28-4.17 (2H, m, OC$\mathbf{H}_2$), 3.61 (2H, t, J = 6.4 Hz, CH$_2$C$\mathbf{H}_2$N), 2.79 (2H, t, J = 6.4 Hz, C$\mathbf{H}_2$CH$_2$N), 2.10 (3H, s, C$\mathbf{H}_3$C=O), 1.33-1.25 (3H, m, OCH$_2$C$\mathbf{H}_3$); (Minor rotamer) δ 7.46 (1H, d, J = 15.4 Hz, =C**H**), 7.37-7.15 (5H, m, Ar**H** and =C**H**), 6.88 (1H, d, J = 15.4 Hz, =C**H**), 4.65 (2H, s, C$\mathbf{H}_2$Ph), 4.28-4.17 (2H, m, OC$\mathbf{H}_2$), 3.63 (2H, t, J = 6.8 Hz, CH$_2$C$\mathbf{H}_2$N), 2.63 (2H, t, J = 6.8 Hz, C$\mathbf{H}_2$CH$_2$N), 2.04 (3H, s, C$\mathbf{H}_3$C=O), 1.33-1.25 (3H, m, OCH$_2$C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 206.8 (C), 205.3 (C), 165.4 (C), 165.3 (C), 165.1 (C), 164.7 (C), 136.9 (C), 136.2 (C), 133.4 (CH), 131.9 (CH), 131.7 (CH), 128.8 (CH), 128.6 (CH), 127.9 (CH), 127.7 (CH), 127.5 (CH), 126.5 (CH), 60.9 (CH_2), 52.4 (CH_2), 49.2 (CH_2), 42.5 (CH_2), 42.2 (CH_2), 41.9 (CH_2), 41.4 (CH_2), 29.9 (CH_3), 29.8 (CH_3), 13.9

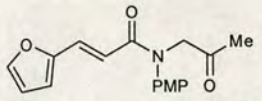
(CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{22}NO_4$ $[M+H]^+$: 304.1543, found: 304.1541.



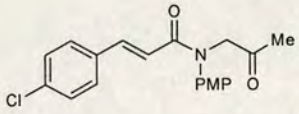
***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-phenylpropenamide (113c)**. Prepared according to a previously reported procedure (Chapter 3.3).



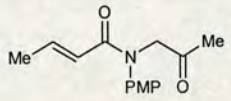
***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-(2-methoxyphenyl)propenamide (131l)**. Prepared according to a previously reported procedure (Chapter 4.3).



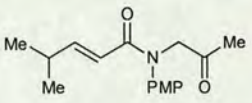
***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-furan-2-ylpropenamide (131m).** Prepared according to a previously reported procedure (Chapter 4.3).



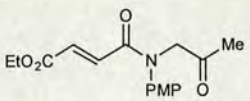
***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-3-(4-chlorophenyl)propenamide (131n).** Prepared according to a previously reported procedure (Chapter 4.3).



***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-but-2-enamide (179a)**. The title compound was prepared according to General Procedure D from the amine **126** (1.05 g, 5.80 mmol) and crotonoyl chloride (834 μL, 8.70 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol) to give a yellow oil (921 mg, 64%). IR (film) 2915, 1731 (C=O), 1665 (C=O), 1628, 1513, 1250, 1030, 967, 842, 686 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 9.0 Hz, Ar**H**), 6.92 (1H, app q, J = 6.9 Hz, $CH_3C\mathbf{H}$=), 6.87 (2H, d, J = 9.0 Hz, Ar**H**), 5.77 (1H, dq, J = 15.1, 1.7 Hz, C**H**C=O), 4.43 (2H, s, $C\mathbf{H}_2N$), 3.80 (3H, s, $OC\mathbf{H}_3$), 2.15 (3H, s, $C\mathbf{H}_3C$=O), 1.72 (3H, dd, J = 6.9, 1.7 Hz, $C\mathbf{H}_3CH$=); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 202.6 (C), 166.2 (C), 158.9 (C), 142.0 (CH), 135.3 (C), 129.2 (2 x CH), 121.8 (CH), 114.5 (2 x CH), 59.6 (CH_2), 55.4 (CH_3), 27.1 (CH_3), 17.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}NO_3$ $[M+H]^+$: 248.1281, found: 248.1279.

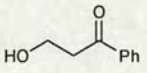


***N*-(4-Methoxyphenyl)-*N*-(2-oxopropyl)-(*E*)-4-methylpent-2-enamide (179b)**. The title compound was prepared according to General Procedure D from the amine **126** (806 mg, 4.50 mmol) and the acid chloride (prepared according to General Procedure A) derived from 4-methyl-2-pentenoic acid (571 mg, 5.00 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol→40% EtOAc/petrol) to give a yellow oil (665 mg, 54%). IR (film) 2961, 1731 (C=O), 1660 (C=O), 1629, 1512, 1380, 1251, 1171, 1031, 841 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.14 (2H, d, J = 8.9 Hz, Ar**H**), 6.83 (2H, d, J = 8.9 Hz, Ar**H**), 6.79 (1H, dd, J = 15.3, 7.1 Hz, C**H**=CHC=O), 5.66 (1H, dd, J = 15.3, 1.3 Hz, CH=C**H**C=O), 4.39 (2H, s, C$\mathbf{H}_2$N), 3.75 (3H, s, OC$\mathbf{H}_3$), 2.24 (1H, septet d, J = 6.8, 1.3 Hz, $(CH_3)_2$C**H**), 2.10 (3H, s, C$\mathbf{H}_3$C=O), 0.87 (6H, d, J = 6.8 Hz, $(\mathbf{CH}_3)_2$CH); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 202.5 (C), 166.4 (C), 158.7 (C), 152.9 (C), 135.1 (C), 129.0 (2 x CH), 117.7 (CH), 114.3 (2 x CH), 59.5 (CH_2), 55.2 (CH_3), 30.8 (CH), 27.0 (CH_3), 21.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_3$ $[M+H]^+$: 276.1594, found: 276.1593.



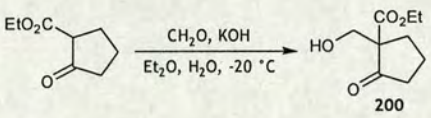
Ethyl (*E*)-3-[*N*-(4-methoxyphenyl)-*N*-(3-oxopropyl)carbamoyl]acrylate (179c). The title compound was prepared according to General Procedure D from the amine **126** (1.07 g, 6.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from mono-ethyl fumarate (1.37 g, 9.00 mmol) for a reaction time of 16 h and purified by column chromatography (50% EtOAc/hexanes) to give a beige solid (1.60 g, 86%). m.p. 49-50 °C; IR ($CHCl_3$) 2981, 1726 (C=O), 1656 (C=O), 1636 (C=C), 1512, 1426, 1030, 842, 735, 603 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.18 (2H, d, J = 8.9 Hz, Ar**H**), 6.90-6.78 (2H, m, C**H**=C**H**), 6.88 (2H, d, J = 8.9 Hz, Ar**H**), 4.49 (2H, s, C$\mathbf{H}_2$N), 4.14 (2H, q, J = 7.1 Hz, OC$\mathbf{H}_2$), 3.80 (3H, s, OC$\mathbf{H}_3$), 2.15 (3H, s, C$\mathbf{H}_3$C=O), 1.22 (3H, t, J = 7.1 Hz, $OCH_2\mathbf{CH}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 201.4 (C), 165.3 (C), 164.2 (C), 159.3 (C), 134.1 (C), 133.2 (CH), 131.4 (CH), 128.8 (2 x CH), 114.8 (2 x CH), 60.8 (CH_2), 59.8 (CH_2), 55.3 (CH_3), 27.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{20}NO_5$ $[M+H]^+$: 306.1336, found: 306.1336.

Preparation of Hydroxyketones



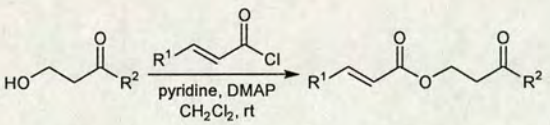
3-Hydroxypropiophenone (199). Prepared according to a previously reported procedure.[27]

1-Hydroxymethyl-2-oxo-cyclopentanecarboxylic acid ethyl ester (200).



To a solution of 2-oxocyclopentanecaboxylate (0.60 mL, 4.00 mmol) and aqueous formaldehyde solution (37 % wt in H_2O, 1.80 mL, 24.0 mmol) in EtOH (20 mL) at –20 °C, was added KOH (673 mg, 12.0 mmol) portionwise over 5 min. The mixture was stirred at –20 °C for 0.5 h, and then poured into saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave the alcohol **200** (432 mg, 58%) that displayed spectroscopic data consistent with those reported previously.

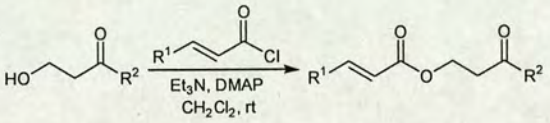
Preparation of Ester-Tethered Cyclization Precursors: General Procedure L



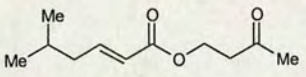
The appropriate α,β-unsaturated acid chloride (neat in the case of commercially available acid chlorides, or as a solution in CH_2Cl_2 prepared according to General Procedure A, 1.1 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate hydroxyketone (1.0 equiv), DMAP (0.05 equiv) and pyridine (4.0 equiv) in CH_2Cl_2 (1.0 M with respect to hydroxyketone) over 5 min *via* cannula, and the reaction was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous

$NaHCO_3$ solution and Et_2O. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution (x 3), dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclization substrate.

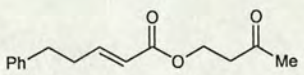
Preparation of Ester-Tethered Cyclization Precursors: General Procedure M



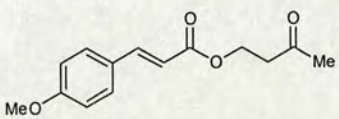
This method was identical to General Procedure L, except that Et_3N (1.5 equiv) was used in place of pyridine.



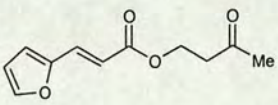
3-Oxobutyl (*E*)-5-methylhex-2-enoate (181a). Prepared according to a previously reported procedure.[27]



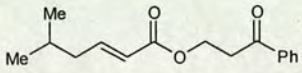
3-Oxobutyl (*E*)-5-phenylpent-2-enoate (181b). Prepared according to a previously reported procedure.[27]



3-Oxobutyl (*E*)-3-(4-methoxyphenyl)propenoate (181c). Prepared according to a previously reported procedure.[27]

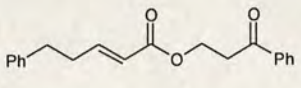


3-Oxobutyl (*E*)-3-furan-2-ylpropenoate (181d). Prepared according to a previously reported procedure.[27]

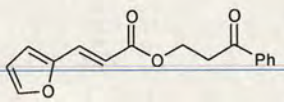


3-Oxo-3-phenylpropyl (*E*)-5-methylhex-2-enoate (181e). The title compound was prepared according to General Procedure L from 3-hydroxypropiophenone **199** (751 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-methylhex-2-enoic acid (705 mg, 5.50 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) to give a colorless oil (600 g, 46%).

IR (film) 2958, 1720 (C=O), 1687 (C=O), 1654 (C=C), 1449, 1265, 1218, 984, 749, 690 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.93 (2H, d, J = 8.0 Hz, Ar**H**), 7.56-7.52 (1H, m, Ar**H**), 7.45-7.41 (2H, m, Ar**H**), 6.94-6.83 (1H, m, C**H**=CHC=O), 5.75 (1H, dd, J = 15.7, 1.3 Hz, C**H**C=O), 4.55 (2H, t, J = 6.4 Hz, C$\mathbf{H}_2$O), 3.32 (2H, t, J = 6.4 Hz, C$\mathbf{H}_2$CH$_2$O), 2.03 (2H, app t, J = 7.1 Hz, CHC$\mathbf{H}_2$CH), 1.77-1.63 (1H, m, $(CH_3)_2$C**H**), 0.87 (6H, d, J = 6.7 Hz, (C$\mathbf{H}_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.0 (C), 166.3 (C), 148.6 (CH), 136.5 (C), 133.2 (CH), 128.5 (2 x CH), 127.9 (2 x CH), 121.7 (CH), 59.4 (CH_2), 41.3 (CH_2), 37.3 (CH_2), 27.6 (CH), 22.2 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{21}O_3$ $[M+H]^+$: 261.1485, found: 261.1489.

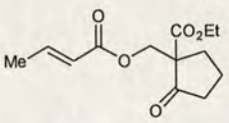


3-Oxo-3-phenylpropyl (*E*)-5-phenylpent-2-enoate (181f). The title compound was prepared according to General Procedure L from 3-hydroxypropiophenone **199** (751 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure A) derived from (*E*)-5-phenylpent-2-enoic acid (969 mg, 5.50 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) to give a colorless oil (926 g, 60%). IR (film) 2925, 1722 (C=O), 1691 (C=O), 1652 (C=C), 1450, 1178, 1088, 976, 750, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.03-8.01 (2H, m, Ar**H**), 7.65-7.61 (1H, m, Ar**H**), 7.54-7.50 (2H, m, Ar**H**), 7.35-7.31 (2H, m, Ar**H**), 7.26-7.20 (3H, m, Ar**H**), 7.05 (1H, dt, J = 15.7, 6.8 Hz, C**H**=CHC=O), 5.88 (1H, dt, J = 15.7, 1.6 Hz, C**H**C=O), 4.64 (2H, t, J = 6.4 Hz, C$\mathbf{H}_2$O), 3.38 (2H, t, J = 6.4 Hz, C$\mathbf{H}_2$CH$_2$O), 2.80 (2H, t, J = 7.8 Hz, PhC$\mathbf{H}_2$), 2.58-2.52 (2H, m, C$\mathbf{H}_2$CH=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.9 (C), 166.2 (C), 148.5 (CH), 140.6 (C), 136.5 (C), 133.2 (CH), 128.5 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 126.0 (CH), 121.3 (CH), 59.4 (CH_2), 37.3 (CH_2), 34.1 (CH_2), 33.7 (CH_2); HRMS (ES) Exact mass calcd for $C_{20}H_{24}NO_3$ $[M+NH_4]^+$: 326.1751, found: 326.1749.

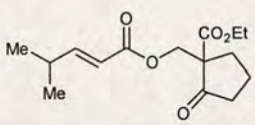


3-Oxo-3-phenylpropyl (*E*)-3-furan-2-ylpropenoate (181g). The title compound was prepared according to General Procedure M from 3-hydroxypropiophenone **199** (1.52 g, 10.0 mmol) and 3-(2-furyl)acrylic acid (1.52 g, 11.0 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) to give a

white solid (1.70 g, 63%). m.p. 85-87 °C; IR (film) 2959, 1707 (C=O), 1637 (C=C), 1448, 1210, 1162, 974, 929, 748, 689 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.02-8.00 (2H, m, Ar**H**), 7.64-7.63 (1H, m, Ar**H**), 7.53-7.49 (3H, m, Ar**H** and C**H**), 7.43 (1H, d, *J* = 15.7 Hz, C**H**=CHC=O), 6.62 (1H, d, *J* = 3.4 Hz, C**H**), 6.48 (1H, dd, *J* = 3.4, 1.8 Hz, C**H**), 6.32 (2H, d, *J* = 15.7 Hz, C**H**C=O), 4.67 (2H, t, *J* = 6.4 Hz, C**H**$_2$O), 3.41 (2H, t, *J* = 6.4 Hz, C**H**$_2$CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 197.0 (C), 166.8 (C), 150.7 (C), 144.7 (CH), 136.6 (C), 133.3 (CH), 131.3 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 115.3 (CH), 114.8 (CH), 112.2 (CH), 59.7 (CH_2), 37.4 (CH_2); HRMS (ES) Exact mass calcd for $C_{16}H_{15}O_4$ $[M+H]^+$: 271.0965, found: 271.0966.

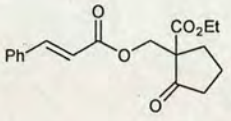


(*E*)-But-2-enoyloxymethyl-2-oxocyclopentanecarboxylic acid ethyl ester (181h). The title compound was prepared according to General Procedure M from the hydroxyketone **200** (152 mg, 0.80 mmol) and *trans*-crotonoyl chloride (0.12 mL, 1.20 mmol) for a reaction time of 22 h and purified by column chromatography (15% EtOAc/petrol) to give a colorless oil (96 mg, 46%). IR (film) 2979, 1755 (C=O), 1727 (C=O), 1657, 1446, 1294, 1261, 1234, 1175, 1029 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.93 (1H, dq, *J* = 15.5, 6.9 Hz, =C**H**), 5.79 (1H, dq, *J* = 15.5, 1.7 Hz, =C**H**), 4.49 (1H, d, *J* =11.1 Hz, CC**H**$_2$O), 4.40 (1H, d, *J* = 11.1 Hz, CC**H**$_2$O), 4.17 (2H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 2.55-1.93 (6H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 1.86 (3H, dd, *J* = 6.9, 1.7 Hz, C**H**$_3$CH=), 1.24 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 212.4 (C), 169.4 (C), 165.8 (C), 145.5 (CH), 122.0 (CH), 64.2 (CH_2), 61.7 (CH_2), 59.6 (C), 38.3 (CH_2), 31.1 (CH_2), 19.7 (CH_2), 18.0 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{19}O_5$ $[M+H]^+$: 255.1227, found: 255.1224.

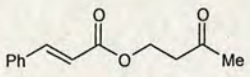


1-[(*E*)-4-Methylpent-2-enoyloxymethyl]-2-oxocyclopentanecarboxylic acid ethyl ester (181i). The title compound was prepared according to General procedure M from the hydroxyketone **200** (500 mg, 2.70 mmol) and the acid chloride (prepared according to General Procedure A) derived from 4-methylpent-2-enoic acid (462 mg, 4.10 mmol) for a reaction time of 43 h and purified by column chromatography (15% EtOAc/petrol) to give a colorless oil (306 mg, 40%). IR (film) 2968, 1754 (C=O),

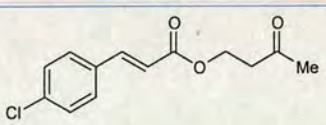
1727 (C=O), 1653, 1458, 1366, 1262, 1155, 1022, 860 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.94 (1H, dd, J = 15.7, 6.6 Hz, =C**H**), 5.73 (1H, dd, J = 15.7, 1.5 Hz, =C**H**), 4.52 (1H, d, J = 11.2 Hz, CC**H**$_2$O), 4.44 (1H, d, J = 11.2 Hz, CC**H**$_2$O), 4.20 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.56-2.41 (3H, m), 2.38-2.28 (1H, m) and 2.20-1.98 (3H, m, C**H**$_2$C**H**$_2$C**H**$_2$ and (CH$_3$)$_2$C**H**), 1.27 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 1.06 (6H, d, J = 6.8 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 212.5 (C), 169.3 (C), 166.4 (C), 156.6 (CH), 117.8 (CH), 64.3 (CH_2), 61.8 (CH_2), 59.7 (C), 38.4 (CH_2), 31.1 (CH_2), 31.0 (CH), 21.1 (2 x CH_3), 19.8 (CH_2), 14.0 (CH_3).



2-Oxo-1-[((*E*)-3-phenylacryloyl)oxymethyl]cyclopentanecarboxylic acid ethyl ester (181j). The title compound was prepared according to General Procedure M from the hydroxyketone **200** (488 mg, 2.60 mmol) and cinnamoyl chloride (655 mg, 3.90 mmol) for a reaction time of 60 h and purified by column chromatography (10% EtOAc/petrol) to give a colorless oil (431 mg, 52%). IR (film) 2979, 1754 (C=O), 1722 (C=O), 1636, 1450, 1309, 1234, 1202, 1154, 1020 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.68 (1H, d, J = 16.0 Hz, =C**H**), 7.54-7.51 (2H, m, Ar**H**), 7.42-7.39 (3H, m, Ar**H**), 6.40 (1H, d, J = 16.0 Hz, =C**H**), 4.62 (1H, d, J = 11.2 Hz, CC**H**$_2$O), 4.51 (1H, d, J = 11.2 Hz, CC**H**$_2$O), 4.22 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.59-2.48 (2H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 2.41-2.32 (1H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 2.24-2.01 (3H, m, C**H**$_2$C**H**$_2$C**H**$_2$), 1.28 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 212.4 (C), 169.2 (C), 166.4 (C), 145.6 (CH), 134.1 (C), 130.5 (CH), 128.9 (2 x CH), 128.1 (2 x CH), 117.2 (CH), 64.5 (CH_2), 61.8 (CH_2), 59.7 (C), 38.4 (CH_2), 31.1 (CH_2), 19.7 (CH_2), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{24}NO_5$ $[M+NH_4]^+$: 334.1649, found: 334.1651.



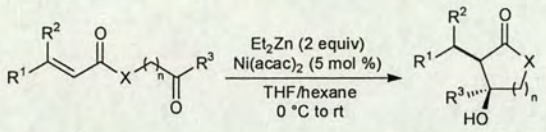
3-Oxobutyl (*E*)-3-phenylpropenoate (183a). Prepared according to a previously reported procedure.[27]



3-Oxobutyl (*E*)-3-(4-chlorophenyl)propenoate (183b). Prepared according to a previously reported

procedure.[27]

Nickel-Catalyzed Reductive Aldol Cyclizations: General Procedure N



A solution of the substrate (0.20 mmol) and $Ni(acac)_2$ (2.7 mg, 0.01 mmol) in THF (1.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 0.40 mL, 0.40 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Nickel-Catalyzed Reductive Aldol Cyclizations: General Procedure O

A solution of the substrate (1.00 mmol) and $Ni(acac)_2$ (13.5 mg, 0.01 mmol) in THF (7.5 mL) was stirred at room temperature for 15 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.0 mL, 2.0 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 1 h and then at room temperature until complete consumption of starting material as observed by TLC analysis. Workup was carried out according to one of the procedures described below.

Workup A

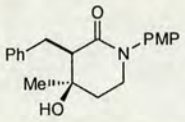
The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.

Workup B

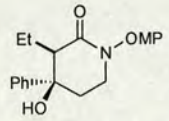
The reaction was quenched carefully by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.

Workup C

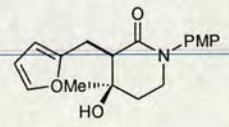
The reaction was quenched carefully by the addition saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclized product.



(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (90l). The title compound was prepared according to General Procedure N from **89l** (65 mg, 0.20 mmol) for a reaction time of 6 h followed by Workup A and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (41 mg, 62%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).

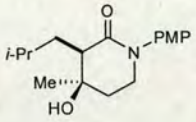


(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-1-(2-methoxyphenyl)-4-phenylpiperidin-2-one (90k). The title compound was prepared according to general procedure N from **89k** (65 mg, 0.20 mmol) for a reaction time of 4 h followed by Workup A and purified by column chromatography (30% EtOAc/$CHCl_3$) to give an off-white solid (41 mg, 62%) that displayed identical spectroscopic data to those reported previously (Chapter 3.3).

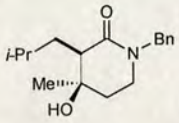


(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (132a). The title compound was prepared according to General Procedure N from **131a** (63 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and

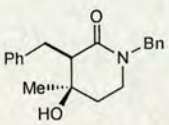
purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (48 mg, 75%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



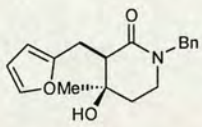
(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpiperidin-2-one (132b). The title compound was prepared according to General Procedure N from **131b** (58 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (20% EtOAc/$CHCl_3$) to give a white solid (41 mg, 70%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



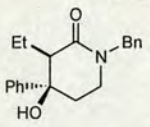
(±)-(3*R*,4*R*)-1-Benzyl-3-*iso*-butyl-4-hydroxy-4-methylpiperidin-2-one (132d). The title compound was prepared according to General Procedure K from **131d** (55 mg, 0.20 mmol) for a reaction time of 8 h using Workup A and purified by column chromatography (50% EtOAc/petrol) to give a white solid (54 mg, 98%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



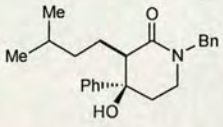
(±)-(3*R*,4*R*)-1,3-Dibenzyl-4-hydroxy-4-methylpiperidin-2-one (132e). The title compound was prepared according to General Procedure N from **131e** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (60% EtOAc/petrol) to give a white solid (60 mg, 97%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



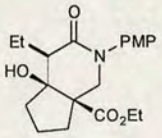
(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-methylpiperidin-2-one (132f). The title compound was prepared according to General Procedure N from **131f** (59 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, >99%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



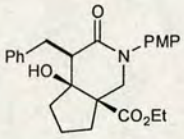
(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-phenylpiperidin-2-one (132g). The title compound was prepared according to General Procedure N from **131g** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (52 mg, 84%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



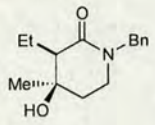
(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3-(3-methylbutyl)-4-phenylpiperidin-2-one (132h). The title compound was prepared according to General Procedure N from **131h** (70 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, 84%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



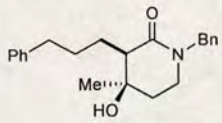
(±)-(1*R*,5*R*,6*S*)-1-Carbethoxy-5-ethyl-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (132j). The title compound was prepared according to General Procedure N from **131j** (72 mg, 0.20 mmol) for a reaction time of 1 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol→50% EtOAc/petrol) to give a colourless oil (45 mg, 62%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



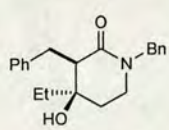
(±)-(1*R*,5*R*,6*S*)-5-Benzyl-1-carbethoxy-6-hydroxy-3-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonan-4-one (132k). The title compound was prepared by General Procedure N from **131k** (84 mg, 0.20 mmol) for a reaction time of 1 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol) to give a colourless oil (43 mg, 50%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



(±)-(3*R*,4*R*)-1-Benzyl-3-ethyl-4-hydroxy-4-methylpiperidin-2-one (171a). The title compound was prepared according to General Procedure N from **170a** (49 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (70% EtOAc/petrol) to give a white solid (48 mg, 97%). m.p. 94-96 °C; IR ($CHCl_3$) 3408 (OH), 2964, 1621 (C=O), 1496, 1453, 1269, 1149, 929, 732, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.23 (5H, m, Ar**H**), 4.64 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 4.51 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 3.39-3.32 (1H, m, C**H**$_2$N), 3.10-3.03 (1H, m, C**H**$_2$N), 2.19 (1H, dd, J = 7.3, 3.8 Hz, CH_2C**H**), 1.96-1.81 (3H, m) and 1.79-1.69 (2H, m, C**H**$_2$$CH_2$N, CH_3C**H**$_2$, and O**H**), 1.30 (3H, s, C**H**$_3$COH), 1.21 (3H, t, J = 7.3 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 137.3 (C), 128.5 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 70.6 (C), 54.2 (CH), 50.0 (CH_2), 43.1 (CH_2), 34.1 (CH_2), 28.3 (CH_3), 20.6 (CH_2), 14.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{21}NO_2[M+H]^+$: 248.1645, found: 248.1645.

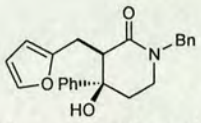


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-(3-phenylpropyl)piperidin-2-one (171c). The title compound was prepared according to General Procedure N from **170c** (67 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (64 mg, 95%). m.p. 120-122 °C; IR ($CHCl_3$) 3410 (OH), 2928, 1620 (C=O), 1496, 1452, 1269, 1142, 931, 734, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34-7.16 (10H, m, Ar**H**), 4.66 (1H, d, J = 14.7 Hz, NC**H**$_2$Ph), 4.50 (1H, d, J = 14.7 Hz, NC**H**$_2$Ar), 3.39-3.31 (1H, m, C**H**$_2$N), 3.10-3.03 (1H, m, C**H**$_2$N), 2.72-2.68 (2H, m, PhC**H**$_2$$CH_2$), 2.29-2.26 (1H, m, CH_2C**H**), 2.18-2.04 (1H, m) and 1.94-1.67 (6H, m, PhCH_2C**H**$_2$C**H**$_2$, C**H**$_2$$CH_2$N and O**H**), 1.27 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.8 (C), 142.4 (C), 137.2 (C), 128.5 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 125.6 (CH), 70.5 (C), 52.5 (CH), 50.0 (CH_2), 43.0 (CH_2), 36.2 (CH_2), 34.1 (CH_2), 31.5 (CH_2), 28.3 (CH_3), 27.1 (CH_2).



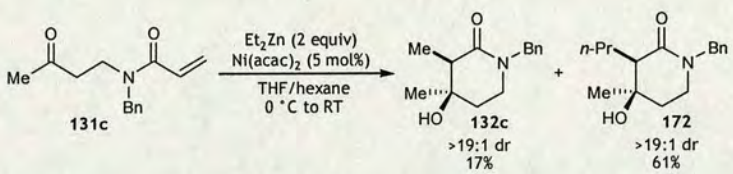
(±)-(3*R*,4*R*)-3-Benzyl-4-ethyl-4-hydroxy-1-(4-methoxyphenyl)piperidin-2-one (171d). The title compound was

prepared according to General Procedure N from **170d** (67 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (40% EtOAc/petrol) to give a white solid (56 mg, 82%) that displayed identical spectroscopic data to those reported previously.[85]



(±)-(3*R*,4*R*)-1-Benzyl-3-furan-2-ylmethyl-4-hydroxy-4-phenylpiperidin-2-one (171e). The title compound was prepared according to General Procedure N from **170e** (72 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (59 mg, 79%). m.p. 120-122 °C; IR ($CHCl_3$) 3398 (OH), 2925, 1624 (C=O), 1495, 1447, 1354, 1073, 911, 758, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.44-7.25 (10H, m, Ar**H**), 7.23 (1H, dd, J = 1.9, 0.8 Hz, C**H**), 6.21 (1H, dd, J = 3.1, 1.9 Hz, C**H**), 5.97 (1H, d, J = 3.1 Hz, C**H**), 4.68 (2H, s, NC**H**$_2$Ph), 3.58 (1H, ddd, J = 11.6, 11.6, 4.8 Hz, C**H**$_2$N), 3.32 (1H, t, J = 5.2 Hz, CH_2C**H**), 3.21 (1H, dd, J = 15.3, 5.2 Hz, C**H**$_2$CH), 3.16-3.10 (1H, m, C**H**$_2$N), 3.01 (1H, dd, J = 15.3, 5.2 Hz, C**H**$_2$CH), 2.59 (1H, br s, O**H**), 2.20 (1H, ddd, J = 13.9, 11.3, 6.1 Hz, C**H**$_2$$CH_2$N), 1.91 (1H, ddd, J = 13.9, 4.8, 2.7 Hz, C**H**$_2$$CH_2$N); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.0 (C), 153.7 (C), 145.4 (C), 140.8 (CH), 137.1 (C), 128.5 (4 x CH), 127.9 (2 x CH), 127.2 (CH), 127.1 (CH), 124.4 (2 x CH), 110.7 (CH), 107.4 (CH), 74.9 (C), 50.6 (CH), 50.5 (CH_2), 43.4 (CH_2), 37.1 (CH_2), 24.7 (CH_2); HRMS (ES) Mass calcd for $C_{23}H_{24}NO_3$ $[M+H]^+$: 362.1751, found: 362.1753.

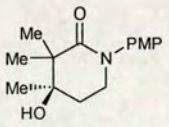
(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-3,4-dimethylpiperidin-2-one (132c) and (±)-(3*R*,4*R*)-1-benzyl-4-hydroxy-4-methyl-3-propylpiperidin-2-one (172).



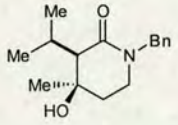
General Procedure N was followed using substrate **131c** (46 mg, 0.20 mmol) for a reaction time of 14 h and the reaction mixture was subjected to Workup A followed by purification by column chromatography (50% EtOAc/petrol) to give the *lactam*

132c (32 mg, 61%) as a white solid, followed by the lactam **172** (8 mg, 17%) as a white solid that displayed identical spectroscopic data to those reported previously.

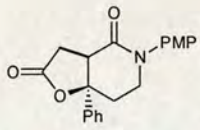
Data for **172**: m.p. 72-74 °C; IR ($CHCl_3$) 3399 (OH), 2959, 1619 (C=O), 1496, 1453, 1266, 1149, 935, 731, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.27 (5H, m, Ar**H**), 4.71 (1H, d, J = 14.6 Hz, NC**H**$_2$Ph), 4.52 (1H, d, J = 14.6 Hz, NC**H**$_2$Ph), 3.41 (1H, ddd, J = 12.3, 7.5, 5.9 Hz, CH_2C**H**$_2$N), 3.12 (1H, ddd, J = 12.3, 6.2, 6.2 Hz, CH_2C**H**$_2$N), 2.29 (1H, dd, J = 6.1, 4.3 Hz, CH_2C**H**), 2.00-1.94 (1H, m, C**H**$_2$$CH_2$N), 1.86-1.69 (4H, m, C**H**$_2$$CH_2$N, CH_3C**H**$_2$ and O**H**), 1.63-1.52 (2H, m, C**H**$_2$CH), 1.34 (3H, s, C**H**$_3$COH), 1.01 (3H, t, J = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.0 (C), 137.3 (C), 128.5 (2 x CH), 128.0 (2 x CH), 127.3 (CH), 70.7 (C), 52.4 (CH), 50.1 (CH_2), 43.1 (CH_2), 34.2 (CH_2), 29.6 (CH_2), 28.3 (CH_3), 23.2 (CH_2), 14.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1802, found: 262.1800.



(±)-(*R*)-4-Hydroxy-1-(4-methoxyphenyl)-3,3,4-trimethylpiperidin-2-one (138a). The title compound was prepared according to General Procedure G from **137a** (52 mg, 0.20 mmol) for a reaction time of 4 h followed by Workup A and purification by column chromatography (20% EtOAc/petrol→30% EtOAc/petrol) to give a white solid (43 mg, 82%). m.p. 104-105 °C; IR ($CHCl_3$) 2978, 1630 (C=O), 1605, 1511, 1329, 1243, 1100, 1035, 827, 668 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.12 (2H, d, J = 9.0 Hz, Ar**H**), 6.89 (2H, d, J = 9.0 Hz, Ar**H**), 3.83 (1H, ddd, J = 15.3, 9.2, 5.8 Hz, CH_2C**H**$_2$N), 3.80 (3H, s, OC**H**$_3$), 3.44 (1H, ddd, J = 12.9, 6.4, 4.6 Hz, CH_2C**H**$_2$N), 2.16 (1H, ddd, J = 15.3, 9.2, 6.4 Hz, C**H**$_2$$CH_2$N), 1.96 (1H, ddd, J = 12.9, 5.8, 4.6 Hz, C**H**$_2$$CH_2$N), 1.78 (1H, br s, O**H**), 1.34 (3H, s, C**H**$_3$), 1.33 (3H, s, C**H**$_3$), 1.30 (3H, s, C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 175.8 (C), 157.9 (C), 136.6 (C), 127.4 (2 x CH), 114.3 (2 x CH), 72.6 (C), 55.4 (CH_3), 47.3 (C), 47.0 (CH_2), 32.2 (CH_2), 24.9 (CH_3), 24.1 (CH_3), 19.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{22}NO_3$ $[M+H]^+$: 264.1598, found: 264.1594.

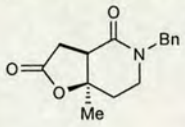


(±)-(3*R*,4*R*)-1-Benzyl-4-hydroxy-4-methyl-3-*iso*-propylpiperidin-2-one (174). The title compound was prepared according to General Procedure G from **173** (52 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (28 mg, 54%). m.p. 108-110 °C; IR ($CHCl_3$) 3408 (OH), 2964, 1621 (C=O), 1496, 1453, 1265, 1147, 926, 737, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36-7.27 (5H, m, Ar**H**), 4.62 (2H, s, C**H**$_2$Ph), 3.41 (1H, ddd, J = 12.5, 6.6, 5.9 Hz, CH_2CH_2N), 3.05 (1H, ddd, J = 12.5, 7.1, 5.9 Hz, CH_2CH_2N), 2.37-2.29 (2H, m, $(CH_3)_2CH$ and CHC=O), 1.96 (1H, ddd, J = 13.4, 7.1, 5.9 Hz, CH_2CH_2N), 1.86 (1H, br s, O**H**), 1.72 (1H, ddd, J = 13.4, 6.6, 5.9 Hz, CH_2CH_2N), 1.32 (3H, s, CH_3COH), 1.32 (3H, d, J = 6.9 Hz, $(CH_3)_2CH$), 1.07 (3H, d, J = 6.8 Hz, $(CH_3)_2CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 170.5 (C), 137.2 (C), 128.4 (2 x CH), 128.2 (2 x CH), 127.2 (CH), 70.9 (C), 57.9 (CH), 49.9 (CH_2), 43.0 (CH_2), 34.1 (CH_2), 29.0 (CH_3), 26.8 (CH), 25.7 (CH_3), 19.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$: 262.1802, found: 262.1802.

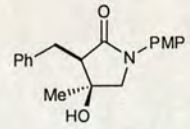


(±)-(3a*R*,7a*R*)-5-(4-Methoxyphenyl)-7a-phenylhexahydrofuro[3,2-*c*]pyridine-2,4-dione (176a). The title compound was prepared according to General Procedure G from **174a** (76 mg, 0.20 mmol) for a reaction time of 18 h followed by Workup A and purification by column chromatography (25% EtOAc/$CHCl_3$→35% EtOAc/$CHCl_3$) to give a white solid (53 mg, 79%). IR ($CHCl_3$) 2930, 1783 (C=O), 1650 (C=O), 1511, 1248, 1031 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47-7.38 (5H, m, Ar**H**), 7.21 (2H, dm, J = 8.7 Hz, Ar**H**), 6.95 (2H, dm, J = 8.7 Hz, Ar**H**), 4.02 (1H, ddd, J = 13.0, 9.3, 5.4 Hz, C**H**$_2$N), 3.83 (3H, s, O**CH**$_3$), 3.63-3.57 (2H, m, C**H**$_2$N and C**H**$_2$CH), 2.99-2.87 (2H, m, C**H**$_2$C**H**), 2.52-2.41 (2H, m, C**H**$_2$$CH_2N$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 168.8 (C), 158.5 (C), 141.3 (C), 135.0 (C), 129.1 (2 x CH), 128.6 (CH), 126.9 (2 x CH), 124.3 (2 x CH), 114.6 (2 x CH), 86.4 (C), 55.5 (CH_3), 47.8 (CH), 47.0 (CH_2), 34.9 (CH_2), 33.6 (CH_2); LRMS (ES) Mass calcd for $C_{20}H_{20}NO_4$ $[M+H]^+$: 338.1, found: 338.1.

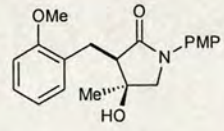
(±)-(3a*R*,7a*R*)-5-Benzyl-7a-methylhexahydrofuro[3,2-*c*]pyridine-2,4-dione



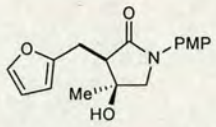
(176b). The title compound was prepared according to General Procedure G from **174b** (61 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup A and purification by column chromatography (50% EtOAc/petrol) to give a white solid (46 mg, 89%). m.p. 114-115 °C; IR ($CHCl_3$) 3510 (OH), 2976, 1778 (C=O), 1643 (C=O), 1496, 1292, 1147, 948, 735, 708 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36-7.27 (3H, m, Ar**H**), 7.24-7.22 (2H, m, Ar**H**), 4.76 (1H, d, J = 14.6 Hz, C**H**$_2$Ph), 4.46 (1H, d, J = 14.6 Hz, C**H**$_2$Ph), 3.42-3.35 (1H, m, CH_2C**H**$_2$N), 3.21-3.14 (2H, m, CH_2C**H**$_2$N and C**H**$_2$CH), 3.04 (1H, dd, J = 10.4, 3.1 Hz, CH_2C**H**), 2.92 (1H, dd, J = 18.1, 3.1 Hz, C**H**$_2$CH), 2.16-2.10 (1H, m, C**H**$_2$$CH_2$N), 1.90 (1H, ddd, J = 14.4, 9.9, 4.6 Hz, C**H**$_2$$CH_2$N), 1.50 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.2 (C), 168.3 (C), 136.0 (C), 128.5 (2 x CH), 127.6 (2 x CH), 127.4 (CH), 83.3 (C), 50.1 (CH), 46.2 (CH), 41.9 (CH_2), 33.8 (CH_2), 32.6 (CH_2), 26.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1281, found: 260.1281.



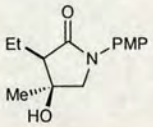
(±)-(3*R*,4*S*)-3-Benzyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (114c). The title compound was prepared according to General Procedure N from **113c** (62 mg, 0.20 mmol) for a reaction time of 24 h followed by Workup A and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (14 mg, 56%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



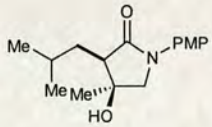
(±)-(3*R*,4*S*)-4-Hydroxy-3-(2-methoxybenzyl)-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (132l). The title compound was prepared according to General Procedure G from **131l** (68 mg, 0.20 mmol) for a reaction time of 4 h followed by Workup A and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (34 mg, 58%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).



(3*R*,4*S*)-3-((furan-2-yl)methyl)-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (132m). The title compound was prepared according to General Procedure K from **131m** (68 mg, 0.20 mmol) for a reaction time of 24 h followed by Workup B and purification by column chromatography (30% EtOAc/$CHCl_3$) to give a white solid (22 mg, 32%) that displayed identical spectroscopic data to those reported previously (Chapter 4.3).

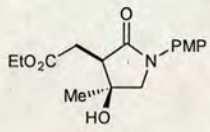


(±)-(3*R*,4*S*)-3-Ethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (180a). The title compound was prepared according to General Procedure G from **179a** (49 mg, 0.20 mmol) for a reaction time of 30 min followed by Workup A and purification by column chromatography (30% EtOAc/petrol) to give a white solid (21 mg, 42%). m.p. 120-122 °C; IR ($CHCl_3$) 3427 (OH), 2964, 1675 (C=O), 1513, 1401, 1248, 1181, 1033, 944, 830 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 9.2 Hz, Ar**H**), 6.89 (2H, d, J = 9.2 Hz, Ar**H**), 3.80 (3H, s, O**CH**$_3$), 3.73 (1H, d, J = 10.3 Hz, **CH**$_2$N), 3.65 (1H, d, J = 10.3 Hz, **CH**$_2$N), 2.31 (1H, t, J = 7.3 Hz, **CH**C=O), 1.98-1.86 (1H, m, CH_3**CH**$_2$), 1.77-1.67 (1H, m, CH_3**CH**$_2$), 1.65 (1H, br s, O**H**), 1.53 (3H, s, **CH**$_3$COH), 1.19 (3H, t, J = 7.3 Hz, **CH**$_3$$CH_2$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 174.0 (C), 156.5 (C), 132.5 (C), 121.5 (2 x CH), 114.0 (2 x CH), 73.3 (C), 60.9 (CH_2), 55.5 (CH), 55.0 (CH_3), 26.0 (CH_3), 17.9 (CH_2), 13.1 (CH_3); HRMS (EI) Exact mass calcd for $C_{14}H_{19}NO_3$ $[M]^+$: 249.1359, found: 249.1358.

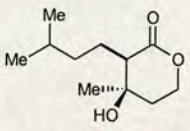


(±)-(3*R*,4*S*)-3-*iso*-Butyl-4-hydroxy-1-(4-methoxyphenyl)-4-methylpyrrolidin-2-one (180b). The title compound was prepared according to General Procedure G from **179b** (55 mg, 0.20 mmol) for a reaction time of 30 min followed by Workup A and purification by column chromatography (30% EtOAc/petrol) to give a white solid (39 mg, 70%). m.p. 124-126 °C; IR ($CHCl_3$) 3426 (OH), 2956, 1674 (C=O), 1513, 1401, 1248, 1181, 1034, 950, 829 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.49 (2H, d, J = 9.2 Hz, Ar**H**), 6.89 (2H, d, J = 9.2 Hz, Ar**H**), 3.80 (3H, s, O**CH**$_3$), 3.75 (1H, d, J = 10.3 Hz, **CH**$_2$N), 3.65 (1H, d, J = 10.3 Hz, **CH**$_2$N), 3.47 (1H, t, J = 6.8 Hz, **CH**C=O), 2.07-

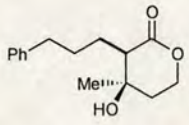
1.96 (1H, m, C**H**$_2$CHC=O), 1.87 (1H, br s, O**H**), 1.78-1.70 (1H, m, C**H**$_2$CHC=O), 1.51-1.43 (1H, m, (CH$_3$)$_2$C**H**), 1.50 (3H, s, C**H**$_3$COH), 1.00 (3H, d, J= 6.6 Hz, (C**H**$_3$)$_2$CH), 0.97 (3H, d, J = 6.6 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (69.2 MHz, CDCl$_3$) δ 174.3 (C), 156.4 (C), 132.6 (C), 121.4 (2 x CH), 114.0 (2 x CH), 73.4 (C), 60.8 (CH_2), 55.4 (CH_3), 50.9 (CH), 33.4 (CH_2), 25.9 (CH), 25.3 (CH_3), 22.6 (CH_3), 22.5(CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_3$ $[M+H]^+$: 278.1751, found: 278.1751.



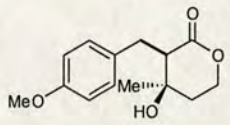
Ethyl [(3*R*,4*S*)-4-Hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxopyrrolidin-3-yl]acetate (180c). The title compound was prepared according to General Procedure G from **179c** (61 mg, 0.20 mmol) for a reaction time of 14 h followed by Workup A and purification by column chromatography (40% EtOAc/petrol) to give a white solid (47 mg, 76%). m.p. 79-81 °C. IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1451, 1269, 1146, 918, 732, 700 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.45 (2H, d, J = 9.1 Hz, Ar**H**), 6.89 (2H, d, J = 9.1 Hz, Ar**H**), 4.48 (1H, br s, O**H**), 4.25-4.17 (2H, m, OC**H**$_2$), 3.88 (1H, d, J = 9.4 Hz, C**H**$_2$N), 3.79 (3H, s, OC**H**$_3$), 3.57 (1H, d, J = 9.4 Hz, C**H**$_2$N), 3.14 (1H, dd, J = 12.1, 3.7 Hz, CH$_2$C**H**), 3.13 (1H, dd, J = 18.7, 3.7 Hz, C**H**$_2$CH), 2.60 (1H, dd, J = 18.7, 12.1 Hz, C**H**$_2$CH), 1.35 (3H, s, C**H**$_3$COH), 1.31 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.1 (C), 170.9 (C), 156.7 (C), 132.0 (C), 121.7 (2 x CH), 114.0 (2 x CH), 72.9 (C), 61.4 (CH_2), 60.2 (CH_2), 55.4 (CH_3), 50.6 (CH), 30.8 (CH_2), 23.3 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$: 308.1492, found: 308.1494.



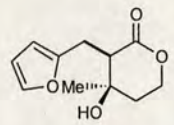
(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-(3-methylbutyl)tetrahydropyran-2-one (182a). The title compound was prepared according to General Procedure N from **181a** (40 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give a colourless oil (31 mg, 77%) that displayed identical spectroscopic data to those reported previously.[27]



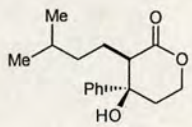
(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-(3-phenylpropyl)tetrahydropyran-2-one (182b). The title compound was prepared according to General Procedure N from **181b** (49 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give a white solid (42 mg, 85%) that displayed identical spectroscopic data to those reported previously.[27]



(±)-(3*R*,4*R*)-4-Hydroxy-3-(4-methoxybenzyl)-4-methyltetrahydropyran-2-one (182c). The title compound was prepared according to General Procedure N from **181c** (50 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (40% EtOAc/petrol) to give a white solid (38 mg, 76%) that displayed identical spectroscopic data to those reported previously.[27]

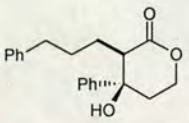


(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-4-methyltetrahydropyran-2-one (182d). The title compound was prepared according to General Procedure N from **181d** (42 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give a white solid (34 mg, 81%) that displayed identical spectroscopic data to those reported previously.[27]

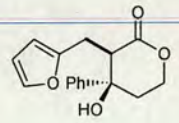


(±)-(3*R*,4*R*)-4-Hydroxy-3-(3-methylbutyl)-4-phenyltetrahydropyran-2-one (181e). General Procedure N was followed using **182e** (52 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give the title compound and its diastereomer as a 5.5:1 inseparable mixture as a white solid (44 mg, 99%). m.p. 116-118 °C; IR ($CHCl_3$) 3366 (OH), 2953, 1703 (C=O), 1447, 1210, 1110, 1065, 934, 755, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.39 (4H, m, Ar**H**), 7.35-7.29 (1H, m, Ar**H**), 4.63 (1H, ddd, J = 11.4, 8.4, 4.9 Hz, C**H**$_2$O), 4.41 (1H, ddd, J = 11.4, 5.7, 5.3 Hz, C**H**$_2$O), 2.80 (1H, dd, J = 8.5, 2.6 Hz, C**H**C=O), 2.43 (1H, ddd, J = 14.7, 8.4, 5.3 Hz, C**H**$_2$CH$_2$O), 2.28 (1H,

br s, OH), 2.13 (1H, ddd, J = 14.7, 5.7, 4.9 Hz, CH_2CH$_2$O), 1.83-1.73 (1H, m, CH_2CH$_2$CHC=O), 1.52-1.41 (1H, m, CH_2CH$_2$CHC=O), 1.39-1.30 (1H, m, CH_2CHC=O), 1.27-1.18 (1H, m, CH_2CHC=O), 1.06-0.94 (1H, m, (CH$_3$)$_2$C**H**), 0.72 (3H, d, J = 6.5 Hz, (CH_3)$_2$CH), 0.70 (3H, d, J = 6.5 Hz, (CH_3)$_2$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 173.3 (C), 145.2 (C), 128.7 (2 x CH), 127.5 (CH), 124.3 (2 x CH), 75.6 (C), 65.1 (CH$_2$), 51.2 (CH), 39.2 (CH$_2$), 38.3 (CH$_2$), 27.8 (CH), 22.9 (CH$_2$), 22.4 (CH$_3$), 22.0 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{16}H_{26}NO_3$ $[M+NH_4]^+$: 280.1907, found: 280.1903.

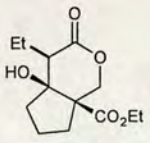


(±)-(3*R*,4*R*)-4-Hydroxy-4-phenyl-3-(3-phenylpropyl)tetrahydropyran-2-one (182f). General Procedure N was followed using **181f** (62 mg, 0.20 mmol) for a reaction time of 8 h followed by Workup B and purification by column chromatography (30% EtOAc/petrol) to give the title compound and the corresponding alkylative aldol cyclization product as a >95:5 inseparable mixture as a white solid (50 mg, 76% (adjusted yield of **176f**)). m.p. 100-102 °C; IR (CHCl$_3$) 3366 (OH), 2953, 1703 (C=O), 1447, 1210, 1110, 1065, 934, 755, 703 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.41-7.38 (4H, m, Ar**H**), 7.35-7.31 (1H, m, Ar**H**), 7.23-7.18 (2H, m, Ar**H**), 7.15-7.11 (1H, m, Ar**H**), 7.03-7.01 (2H, m, Ar**H**), 4.62 (1H, ddd, J = 11.5, 8.7, 4.8 Hz, CH_2O), 4.40 (1H, ddd, J = 11.5, 5.5, 5.5 Hz, CH_2O), 2.84 (1H, dd, J = 8.3, 2.7 Hz, C**H**C=O), 2.46 (2H, t, J = 7.7 Hz, PhCH_2), 2.43 (1H, ddd, J = 14.2, 8.7, 5.5 Hz, CH_2CH$_2$O), 2.31 (1H, br s, OH), 2.10 (1H, ddd, J = 14.2, 5.5, 4.8 Hz, CH_2CH$_2$O), 2.00-1.79 (2H, m, CH_2CH$_2$CHC=O), 1.50-1.42 (1H, m, CH_2CHC=O), 1.34-1.25 (1H, m, CH_2CHC=O); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 173.3 (C), 145.0 (C), 141.9 (C), 128.7 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.5 (CH), 125.6 (CH), 124.3 (2 x CH), 75.4 (C), 65.1 (CH$_2$), 51.0 (CH), 39.1 (CH$_2$), 35.5 (CH$_2$), 30.5 (CH$_2$), 24.9 (CH$_2$); HRMS (ES) Exact mass calcd for $C_{20}H_{26}NO_3$ $[M+NH_4]^+$: 328.1907, found: 328.1906.

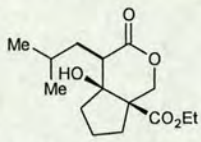


(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-4-phenyltetrahydropyran-2-one (182g). General Procedure N was follwed using **181g** (54 mg, 0.20 mmol) for a reaction time of 8 h

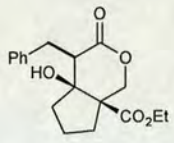
followed by Workup B and purification by column chromatography (70% EtOAc/petrol) to give the title compound and the corresponding alkylative aldol cyclization product as a 9:1 inseparable mixture as white solid (46 mg, 75% (adjusted yield of **182g**)). m.p. 108-110 °C; IR ($CHCl_3$) 3436 (OH), 2972, 1727 (C=O), 1447, 1408, 1266, 1198, 1011, 754, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.45-7.38 (4H, m, Ar**H**), 7.33-7.27 (1H, m, Ar**H**), 7.20 (1H, dd, J = 1.9, 0.8 Hz, C**H**), 6.19 (1H, dd, J = 3.2, 1.9 Hz, C**H**), 5.96 (1H, dd, J = 3.2, 0.8 Hz, C**H**), 4.67 (1H, ddd, J = 11.4, 9.6, 4.6 Hz, C**H**$_2$O), 4.42 (1H, ddd, J = 11.4, 5.5, 4.6 Hz, C**H**$_2$O), 3.39 (1H, dd, J = 6.5, 4.5 Hz, C**H**C=O), 3.07 (1H, dd, J = 15.5, 6.5 Hz, C**H**$_2$CH), 2.93 (1H, dd, J = 15.5, 4.5 Hz, C**H**$_2$CH), 2.72 (1H, br s, O**H**), 2.43 (1H, ddd, J = 14.7, 9.6, 5.5 Hz, C**H**$_2$CH$_2$O), 2.08 (1H, ddd, J = 14.7, 9.6, 5.5 Hz, C**H**$_2$CH$_2$O); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.9 (C), 152.7 (C), 144.4 (C), 141.0 (CH), 128.7 (2 x CH), 127.5 (CH), 124.3 (2 x CH), 110.7 (CH), 107.4 (CH), 75.0 (C), 65.3 (CH_2), 50.2 (CH), 39.5 (CH_2), 23.9 (CH_2); HRMS (ES) Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$: 273.1121, found: 273.1120.



(±)-(1*R*,5*R*,6*S*)-1-Carbethoxy-5-ethyl-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (182h). The title compound was prepared according to General Procedure N from **181h** (51 mg, 0.20 mmol) for a reaction time of 3.5 h followed by Workup C and purification by column chromatography (30% EtOAc/petrol) to give a colorless oil (45 mg, 88%). IR (film) 3489 (OH), 2972, 1734 (C=O), 1467, 1329, 1305, 1270, 1186, 1134, 1061 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.68 (1H, d, J = 12.1 Hz, CC**H**$_2$O), 4.22 (2H, q, J = 7.2 Hz, OC**H**$_2$CH$_3$), 3.97 (1H, d, J = 12.1 Hz, CC**H**$_2$O), 3.62 (1H, s, O**H**), 2.37 (1H, dd, J = 9.3, 2.7 Hz, CH$_2$C**H**), 2.33-2.21 (1H, m), 2.16-1.88 (4H, m), and 1.73-1.58 (3H, m, C**H**$_2$C**H**$_2$C**H**$_2$ and C**H**$_2$CH), 1.28 (3H, t, J = 7.2 Hz, OCH$_2$C**H**$_3$), 1.05 (3H, t, J = 7.4 Hz, C**H**$_3$CH$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.1 (C), 172.5 (C), 85.0 (C), 69.2 (CH_2), 61.9 (CH_2), 56.5 (C), 50.4 (CH), 41.5 (CH_2), 35.0 (CH_2), 23.4 (CH_2), 18.1 (CH_2), 14.0 (CH_3), 13.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{24}NO_5$ $[M+NH_4]^+$: 274.1649, found: 274.1647.

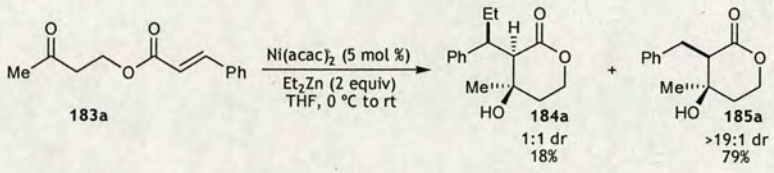


(±)-(1*R*,5*R*,6*S*)-5-*Iso*-butyl-1-carbethoxy-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (182i). The title compound was prepared according to General Procedure N from **181i** (56 mg, 0.20 mmol) for a reaction time of 21 h followed by Workup C and purification by column chromatography (10% EtOAc/petrol→30% EtOAc/petrol) to give a colorless oil (42 mg, 74%). IR (film) 3489 (OH), 2957, 2871, 1740 (C=O), 1469, 1369, 1302, 1249, 1175, 1118 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.72 (1H, d, J = 12.1 Hz, CCH_2O), 4.24 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.00 (1H, d, J = 12.1 Hz, CCH_2O), 3.58 (1H, d, J = 1.0 Hz, O**H**), 2.52 (1H, dd, J = 9.2, 1.6 Hz, C**H**C=O), 2.33-2.24 (1H, m), 2.13-2.04 (2H, m), 1.99-1.90 (2H, m), 1.77-1.61 (3H, m) and 1.37-1.30 (1H, m, $CH_2CH_2CH_2$ and $(CH_3)_2CHCH_2$), 1.30 (3H, t, J = 7.1 Hz, OCH_2CH_3), 0.98 (3H, d, J = 6.6 Hz, $(CH_3)_2CH$), 0.88 (3H, d, J = 6.6 Hz, $(CH_3)_2CH$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ174.1 (C), 172.7 (C), 85.2 (C), 69.2 (CH_2), 62.0 (CH_2), 56.4 (C), 46.1 (CH), 41.5 (CH_2), 35.1 (CH_2), 33.7 (CH_2), 26.5 (CH), 23.4 (CH_3), 23.3 (CH_2), 21.6 (CH_3), 14.0 (CH_3).



(±)-(1*R*,5*R*,6*S*)-5-Benzyl-1-carbethoxy-6-hydroxy-3-oxabicyclo[4.3.0]nonan-4-one (182j). The title compound was prepared according to General Procedure N from **181j**(63 mg, 0.20 mmol) for a reaction time of 2 h followed by Workup C and purification by column chromatography (30% EtOAc/petrol) to give a colorless oil (47 mg, 73%). IR (film) 3481 (OH), 2967, 1739 (C=O), 1454, 1394, 1368, 1305, 1240, 1126, 1043 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.34-7.26 (4H, m, Ar**H**), 7.22-7.18 (1H, m, Ar**H**), 4.69 (1H, d, J = 12.1 Hz, CCH_2O), 4.26 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.95 (1H, d, J = 12.1 Hz, CCH_2O), 3.90 (1H, d, J = 0.9 Hz, O**H**), 3.41 (1H, dd, J = 14.6, 8.0 Hz, CH_2CH), 2.98 (1H, dd, J = 14.6, 3.4 Hz, CH_2CH), 2.79 (1H, dd, J = 8.0, 3.4 Hz, CH_2CH), 2.32-2.12 (2H, m, $CH_2CH_2CH_2$), 1.98-1.89 (2H, m, $CH_2CH_2CH_2$), 1.69-1.58 (2H, m, $CH_2CH_2CH_2$), 1.32 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.2 (C), 172.1 (C), 140.8 (C), 129.2 (2 x CH), 128.4 (2 x CH), 126.2 (CH), 85.2 (C), 69.2 (CH_2), 62.2 (CH_2), 56.6 (C), 51.1 (CH), 41.8 (CH_2), 35.0 (CH_2), 30.9 (CH_2), 23.4 (CH_2), 14.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{18}H_{22}O_5$ $[M]^+$: 318.1462, found: 318.1463.

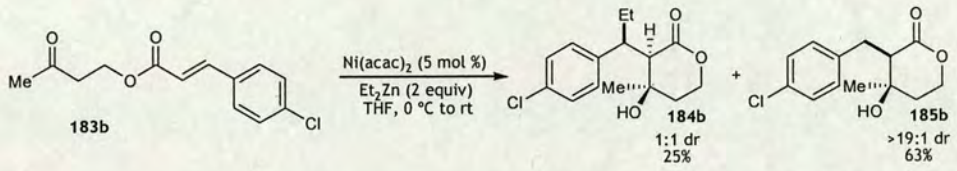
(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-[(*RS*)-1-phenylpropyl]tetrahydropyran-2-one (184a) and (±)-(3*R*,4*R*)-3-benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (185a)



General Procedure N was followed using substrate **183a** (218 mg, 1.00 mmol) for a reaction time of 16 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (20% EtOAc/petrol) to give the *lactone* **184a** (45 mg, 18%) as a 1:1 mixture of diastereomers as a colourless gum, followed by the lactone **185a** (174 mg, 79%) as a white solid that displayed identical spectroscopic data to those reported previously.

Data for **184a** (1:1 mixture of diastereomers): IR ($CHCl_3$) 3436 (OH), 2967, 1709 (C=O), 1454, 1262, 1149, 1120, 1073, 766, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.47-7.24 (5H, m, Ar**H**), 4.60 (0.5H, ddd, J = 11.4, 8.0, 4.8 Hz, C**H**$_2$O), 4.32-4.13 (1.5H, m, C**H**$_2$O), 3.29-3.23 (0.5H, m, CH_2C**H**), 3.18-3.12 (0.5H, m, CH_2C**H**), 2.90 (1H, d, J = 4.0 Hz, C**H**C=O), 2.32-2.17 (0.5H, m, C**H**$_2$$CH_2$O), 2.08-1.71 (4.5H, m, C**H**$_2$$CH_2$O, CH_3C**H**$_2$ and O**H**), 1.43 (1.5H, s, C**H**$_3$COH), 1.39 (1.5H, s, C**H**$_3$COH), 0.86 (1.5H, t, J = 7.3 Hz, C**H**$_3$$CH_2$), 0.77 (1.5H, t, J = 7.3 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.6 (C), 171.4 (C), 144.4 (C), 142.2 (C), 129.5 (CH), 128.8 (CH), 128.7 (CH), 128.6 (CH), 127.1 (CH), 126.6 (CH), 71.1 (C), 70.9 (C), 65.1 (CH_2), 65.0 (CH_2), 58.6 (CH), 57.0 (CH), 46.2 (CH), 45.3 (CH), 36.4 (CH_2), 35.7 (CH_2), 29.7 (CH_3), 29.5 (CH_3), 29.3 (CH_2), 26.9 (CH_2), 12.8 (CH_3), 12.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{24}NO_3$ $[M+NH]^+$: 266.1751, found: 266.1750.

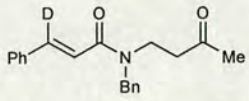
(±)-(3*R*,4*R*)-4-Hydroxy-4-methyl-3-[(*RS*)-1-(4-chlorophenyl)propyl]tetrahydropyran-2-one (184b) and (±)-(3*R*,4*R*)-3-(4-chlorobenzyl)-4-hydroxy-4-methyltetrahydropyran-2-one (185b)



General Procedure N was followed using substrate **183b** (253 mg, 1.00 mmol) for a reaction time of 8 h and the reaction mixture was subjected to Workup B followed by purification by column chromatography (20% EtOAc/petrol) to give the *lactone* **184b** (71 mg, 25%) as a 1:1 mixture of diastereomers as a white solid, followed by the lactone **185b** (160 mg, 63%) as a white solid that displayed identical spectroscopic data to those reported previously.

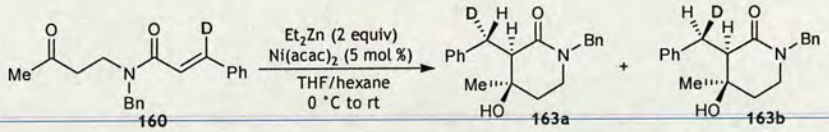
Data for **184b** (1:1 mixture of diastereomers): m.p. 77-79 °C; IR ($CHCl_3$) 3430 (OH), 2931, 1708 (C=O), 1492, 1408, 1262, 1210, 1093, 1014, 830 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.40 (1H, m, Ar**H**), 7.37-7.29 (3H, m, Ar**H**), 4.60 (0.5H, ddd, J = 11.4, 8.5, 4.7 Hz, C**H**$_2$O), 4.31-4.12 (1.5H, m, C**H**$_2$O), 3.29-3.24 (0.5H, m, CH$_2$C**H**), 3.14-3.09 (0.5H, m, CH$_2$C**H**), 2.87 (0.5H, d, J = 3.3 Hz, C**H**C=O), 2.77 (0.5H, d, J = 3.4 Hz, C**H**C=O), 2.24-2.11 (0.5H, m, C**H**$_2$CH$_2$O), 2.06-1.69 (4.5H, m, C**H**$_2$CH$_2$O, CH$_3$C**H**$_2$ and O**H**), 1.43 (1.5H, s, C**H**$_3$COH), 1.42 (1.5H, s, C**H**$_3$COH), 0.83 (1.5H, t, J = 7.3 Hz, C**H**$_3$CH$_2$), 0.77 (1.5H, t, J = 7.3 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.4 (C), 171.3 (C), 143.4 (C), 140.7 (C), 132.7 (C), 132.0 (C), 130.9 (2 x CH), 130.1 (C), 128.7 (2 x CH), 128.6 (2 x CH), 70.9 (C), 70.0 (C), 65.2 (CH$_2$), 64.9 (CH$_2$), 58.3 (CH), 57.1 (CH), 45.4 (CH), 44.6 (CH), 36.4 (CH$_2$), 35.6 (CH$_2$), 29.6 (CH$_3$), 29.5 (CH$_3$), 29.3 (CH$_2$), 26.4 (CH$_2$), 12.7 (CH$_3$), 12.6 (CH$_3$); HRMS (ES) Exact mass calcd for $C_{15}H_{23}ClNO_3$ $[M+NH_4]^+$: 300.1361, found: 300.1362.

Preparation and Cyclization of Deuterium-Labeled Substrate 154



***N*-Benzyl-*N*-(3-oxobutyl)-(*E*)-3-deuterio-3-phenylpropenamide (160).** The title compound was prepared according to General Procedure I from methyl vinyl ketone (361 μL, 4.00 mmol), benzylamine (393 μL, 3.60 mmol) and the acid chloride (prepared according General Procedure A) derived from *(E)*-3-deuteriocinnamic acid (603 mg, 3.60 mmol) for a reaction time of 16 h and purified by column chromatography (40% EtOAc/petrol) to give light yellow solid (518 mg, 47%) as a 2:1 mixture of rotamers. m.p. 54-56 °C; IR ($CHCl_3$) 2923, 1713 (C=O), 1638 (C=O), 1600 (C=C), 1496, 1370, 1206, 1162, 871, 734, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) (Major rotamer) δ 7.47 (2H, d, J = 5.6 Hz, Ar**H**), 7.42-7.26 (8H, m, Ar**H**), 6.86 (1H, s, =C**H**), 4.79 (2H, s, C**H**$_2$Ph), 3.72 (2H, t, J = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.89 (2H, t, J = 6.7 Hz, C**H**$_2CH_2N$), 2.16 (3H, s, C**H**$_3$C=O); (Minor rotamer) δ 7.59 (2H, d, J = 6.3 Hz, Ar**H**), 7.42-7.26 (8H, m, Ar**H**), 7.01 (1H, s, =C**H**), 4.75 (2H, s, C**H**$_2$Ph), 3.76 (2H, t, J = 6.7 Hz, $CH_2C\mathbf{H}_2N$), 2.73 (2H, t, J = 6.7 Hz, C**H**$_2CH_2N$), 2.11 (3H, s, C**H**$_3$C=O); ^{13}C NMR (90.6 MHz, $CDCl_3$) (Mixture of rotamers – not fully assigned) δ 207.2 (C), 205.9 (C), 166.9 (C), 166.3 (C), 137.5 (CH, t, J_D = 20.4 Hz), 137.0 (CH, t, J_D = 23.7 Hz), 134.9 (C), 134.8 (C), 129.5 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.9 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 126.3 (CH), 117.0 (CH), 116.7 (CH), 52.1 (CH_2), 49.3 (CH_2), 42.7 (CH_2), 42.4 (CH_2), 41.7 (2 x CH_2), 30.1 (CH_3), 29.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{21}DNO_2$ $[M+H]^+$: 309.1708, found: 309.1707.

(±)-(3*R*,4*R*)-1-Benzyl-3-[(*RS*)-deuteriophenylmethyl]-4-hydroxy-4-methylpiperidin-2-one (163).



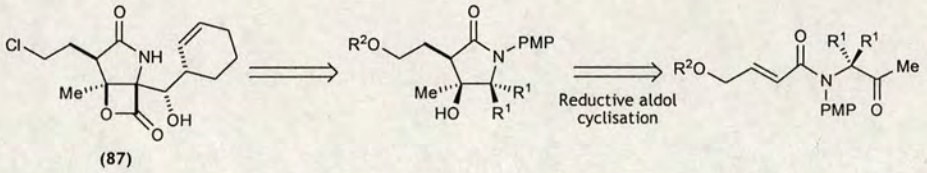
1:1.3 mixture before purification
(Relative stereochemistries of major and minor isomers not assigned)

General Procedure N was followed using substrate **160** (62 mg, 0.20 mmol) for a reaction time of 16 h followed by Workup A to give **163** as a 1:1.3 inseparable mixture of diastereomers. Purification of the residue by column chromatography (70% EtOAc/petrol) gave **163** as a white solid (52 mg, 84%) as a 1:1.5 inseparable mixture of diastereomers. m.p. 114-116 °C; IR ($CHCl_3$) 3399 (OH), 2928, 1617 (C=O), 1495, 1451, 1269, 1146, 918, 732, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.41 (2H, m, Ar**H**), 7.39-7.29 (7H, m, Ar**H**), 7.26-7.21 (1H, m, Ar**H**), 4.75 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 4.58 (1H, d, J = 14.7 Hz, C**H**$_2$Ph), 3.47 (1H, ddd, J = 12.2, 9.0, 5.6 Hz, CH_2C**H**$_2$N), 3.35 (0.4H, d, J = 5.3 Hz, C**H**D), 3.22 (0.6H, d, J = 5.4 Hz, C**H**D), 3.13 (1H, ddd, J = 12.2, 5.9, 5.1 Hz, CH_2C**H**$_2$N), 2.72 (1H, d, J = 5.4 Hz, C**H**CH=O), 1.92-1.80 (2H, m, C**H**$_2$$CH_2$N), 1.76 (1H, br s, O**H**), 1.31 (3H, s, C**H**$_3$COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 171.1 (C), 141.9 (C), 137.1 (C), 129.2 (2 x CH), 128.5 (2 x CH), 128.4 (2 x CH), 127.9 (2 x CH), 127.2 (CH), 126.0 (CH), 71.0 (C), 54.2 (CH), 50.4 (CH_2), 43.0 (CH_2), 35.2 (CH_2), 32.5 (**C**HD, t, J_D = 19.5 Hz), 28.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{23}DNO_2$ $[M+H]^+$: 311.1864, found: 311.1862.

6. Enantioselective Synthesis of Pyrrolidin-2-ones

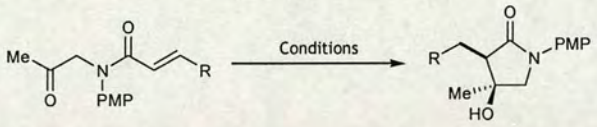
As mentioned previously (Chapter 3), the stereoselective synthesis of heterocyclic ring systems present a particular challenge to synthetic chemists. These structural motifs often appear at the core of important biologically active natural products and pharmaceutical agents, such as salinosporamide A **(87)**[70] and morphine **(88)**(Figure 3.1).

In recent years our group has been interested in developing a novel and efficient synthesis of the marine natural product salinosporamide A **(87)**.[70] The main focus of our research has centred on the development of a reductive aldol methodology which will allow the construction of the γ-lactam core in a highly stereocontrolled manner (Scheme 6.1).



Scheme 6.1

We envisioned that through the development of appropriate conditions, a variety of α,β-unsaturated carbonyl compounds tethered to ketones through an amide linkage would cyclise to provide a number of pyrrolidin-2-one products, which are structurally similar to the core of **(87)** (eq 51).

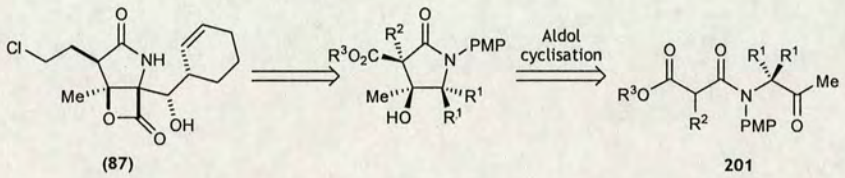


(51)

Under our previously described copper-catalysed conditions the reductive aldol cyclisation of substrates **113** was extremely inefficient (eq. 24-26). On the other hand, the application of our cobalt- (Table 4.2, entries 13-17) and nickel-catalysed

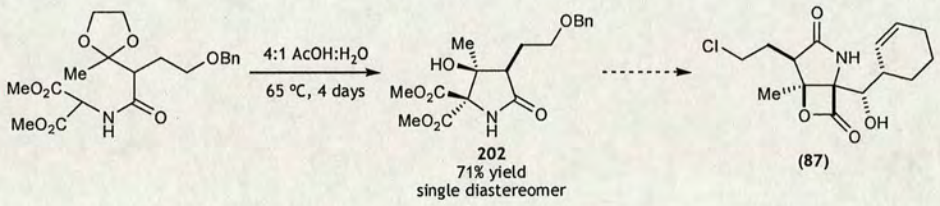
(Table 5.2) conditions allowed the construction of a number of pyrrolidin-2-one products **132** and **180** to be accomplished in moderate yield and with generally good levels of diastereoselectivity; however, all efforts to develop an enantioselective variant of these processes failed.

As a consequence, we considered an alternative strategy for the stereoselective synthesis of γ-lactams involving the cyclisation of a substituted malonate unit on to a tethered methyl ketone acceptor **201** (Scheme 6.2).



Scheme 6.2

In a similar vein, Pattenden and co-workers elegantly demonstrated that the core γ-lactam of **(87)** could be constructed in 71% yield *via* tandem ketone deprotection followed by sequential aldol cyclisation to give the product as a single diastereomer **202** (Scheme 6.3).[71d]



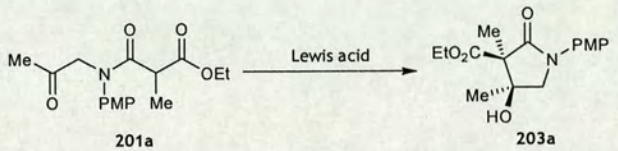
Scheme 6.3

Although this type of intramolecular aldol addition of a substituted malonate unit to a tethered ketone has received little attention in the literature, we surmised that through the development of appropriate conditions the cyclisation of malonates **201** could be accomplished stereoselectively (Scheme 6.2).

6.1. Results and Discussion

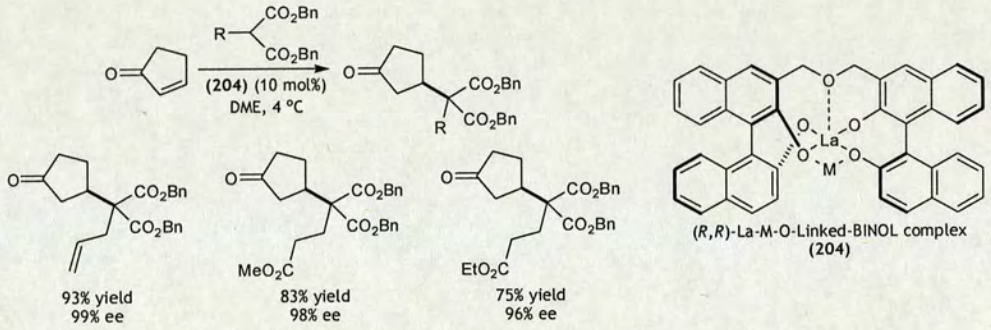
6.1.1. Lewis-acid Mediated Cyclisations

We initially considered the synthesis of pyrrolidin-2-ones *via* a Lewis acid-catalysed cyclisation of substituted malonate derivative **201a** (eq 52).



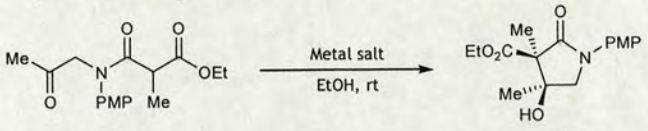
201a **203a** (52)

Such transformations have not been reported in the literature to the best of our knowledge; however, the related conjugate addition of malonates to α,β-unsaturated ketones involving a number of Lewis-acidic catalyst species is well documented (Scheme 6.4).[90]



Scheme 6.4

Therefore, we began by assessing the suitability of several potential Lewis acid promoters in the presence of additional base (Table 6.1).



201a 203a

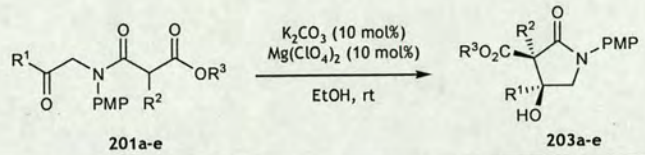
Entry	Metal Salt	mol%	Base	mol%	Time (h)	Conversion%[a]
1	$La(OTf)_3 \cdot xH_2O$	10	K_2CO_3	133	1	100
2	$La(OTf)_3 \cdot xH_2O$	10	-	-	48	0
3	$Yb(OTf)_3 \cdot xH_2O$	10	K_2CO_3	133	1	50
4	$Yb(OTf)_3 \cdot xH_2O$	10	-	-	48	0
5	$Mg(ClO_4)_2$	10	K_2CO_3	133	1	100
6	$Mg(ClO_4)_2$	10	K_2CO_3	10	3	100
7	$Mg(ClO_4)_2$	10	-	-	48	0
8	$Zn(OTf)_2$	10	K_2CO_3	133	48	0
9	$Zn(OTf)_2$	10	-	-	48	0
10	$Ni(acac)_2$	10	K_2CO_3	133	48	0
11	$Sn(OTf)_2$	10	K_2CO_3	133	48	0

[a]Determined by ^1H NMR analysis of the unpurified reaction mixtures

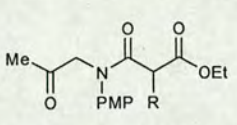
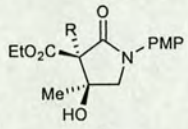
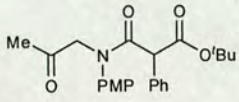
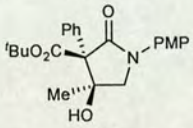
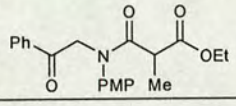
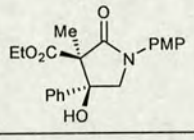
Table 6.1

It was observed that in the absence of additional base the reaction failed to initiate and no product **203a** was formed when substoichiometric quantities of $La(OTf)_3 \cdot xH_2O$ and $Yb(OTf)_3 \cdot xH_2O$ were used (entries 2 and 4). Nevertheless, the addition of 1.33 eq of K_2CO_3 resulted in the formation of the aldol product **203a** as a 1:1 mixture of diastereomers (entries 1 and 3); with $La(OTf)_3 \cdot xH_2O$ proving to be the more effective catalyst, giving the product **203a** in 100% conversion after 1 hour (entry 1). Similarly, the use of substoichiometric quantities of $Mg(ClO_4)_2$ is only effective in the presence of K_2CO_3 (entries 5 and 6); however, in this case the amount of K_2CO_3 can be lowered to 10 mol% with no loss in conversion (entry 6). Alternative Lewis acid promoters such as, $Zn(OTf)_2$, $Ni(acac)_2$ and $Sn(OTf)_2$ proved to be ineffective even in combination with the additional base (entries 8, 10 and 11). Replacing K_2CO_3 with organic bases such as Et_3N, $^iPr_2EtN$ or 2,6-lutidine resulted in negligible substrate conversion, while alternative solvents such as THF, DCM or toluene proved inferior to EtOH in terms of reaction turn-over.

Following the development of an effective $Mg(ClO_4)_2/K_2CO_3$ catalyst combination the scope of the reaction was next investigated (Table 6.2).



201a-e 203a-e

Entry	Substrate		Product		dr	%Conversion[a]
1		R = Me **201a**		**203a**	1:1	100
2		R = Ph **201b**		**203b**	3:1	100
3		R = Bn **201c**		**203c**	-	<10
4		**201d**		**203d**	5:1	100
5		**201e**		**203e**	-	<5

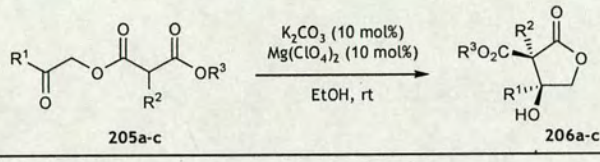
[a]Determined by ^1H NMR analysis of the unpurified reaction mixtures

Table 6.2

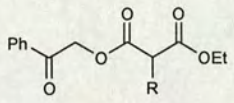
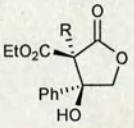
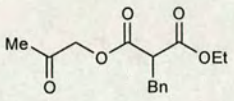
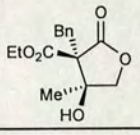
Substrates containing methyl ketones tethered to the malonate unit underwent the most productive cyclisations (entries 1, 2 and 4), giving the corresponding *β*-hydroxylactams **203a, 203b** and **203d** in 100% conversion and with diastereoselectivities of 1:1, 3:1 and 5:1 respectively. However, under these conditions, the attempted cyclisation of substrate **203c** resulted in a mixture of unidentified side-products. Furthermore, replacement of the methyl ketone with a phenyl ketone **203e**led to negligible cyclisation under these conditions (entry 5). This is most likely due to the decreased electrophilicity of aryl ketones compared with alkyl ketones.

Subsequently, the scope of this process was further explored by applying our magnesium catalyst system to the cyclisation of substituted malonate units tethered to ketones *via* an ester linkage (Table 6.3). One would except that due to the decreased electron-donation from the ester tether in substrates **205** compared with

that of the amide tether in substrates **201**, that the deprotonation of the malonate unit and thus cyclisation should occur more readily for those substrates incorporating an ester linkage.



205a-c **206a-c**

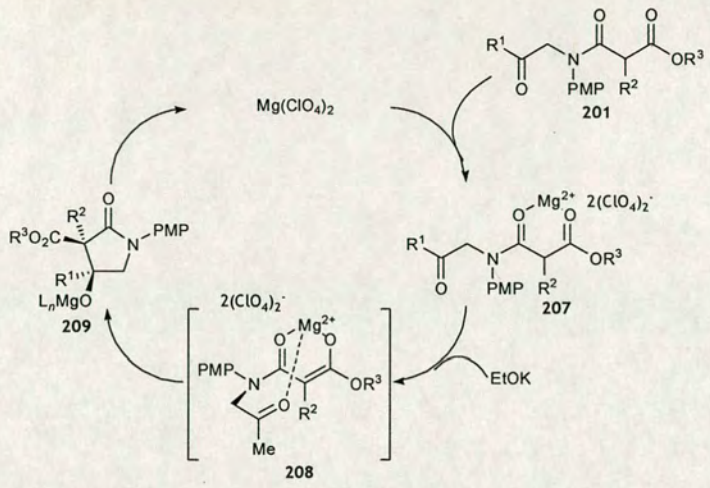
Entry	Substrate		Product		d.r	%Conversion[a]
1		R = Me **205a**		**206a**	-	<5
2		R = Bn **205a**		**206b**	-	<5
3		**205c**		**206c**	-	<5

[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures

Table 6.3

In the event, ester tethered substrates failed to undergo any observable cyclisation and only starting material was recovered from the reaction mixture (entries 1-3). It could be reasoned that the increased electron-donation from the amide linkage is in fact facilitating the coordination of the Lewis acid catalyst, therefore, allowing more efficient activation of the malonate proton towards deprotonation.

At this stage, lacking any literature president, only a speculative mechanistic rationale can be suggested (Scheme 6.5).



Scheme 6.5

Initial coordination of $Mg(ClO_4)_2$ with substrate **201** is followed by deprotonation by potassium ethoxide (formed by the deprotonation of ethanol by K_2CO_3) to produce magnesium enolate intermediate **207**. Rapid aldol cyclisation of **207** will provide the product as a magnesium alkoxide **209** which would then be rapidly protonated by ethanol. If this mechanism is indeed operative then the participation of magnesium enolate **209** in the bond forming event would seem to indicate that a careful choice of chiral non-racemic ligand may lead to an asymmetric variant of this process.

In this regard the cyclisation of substrate **201a** was evaluated in the presence of a variety of chiral non-racemic ligands (Table 6.4).

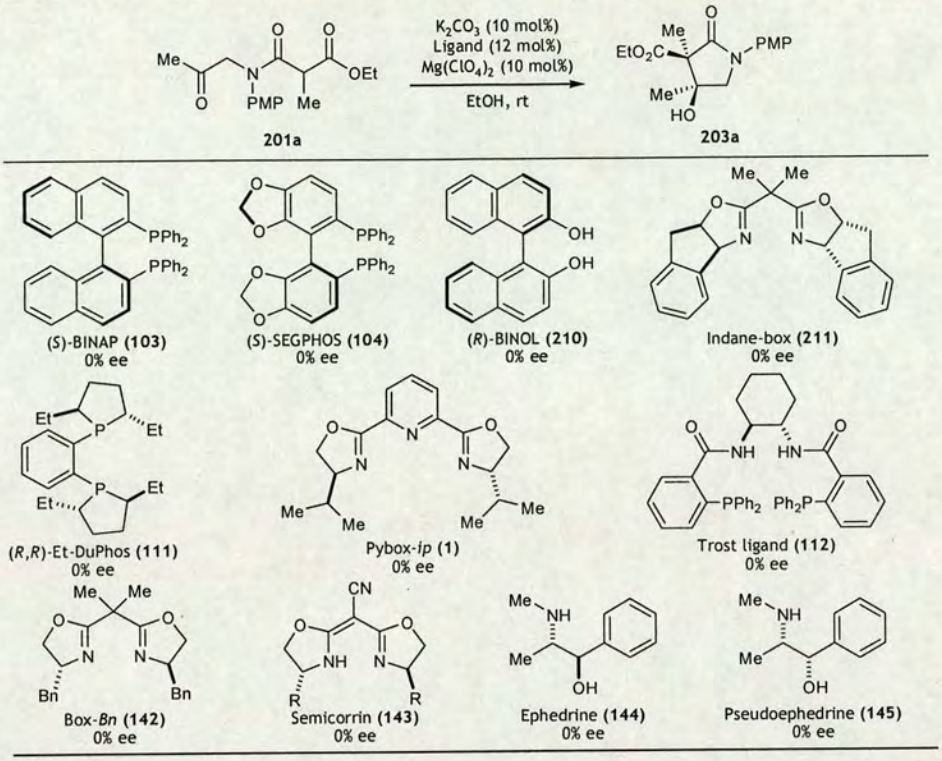
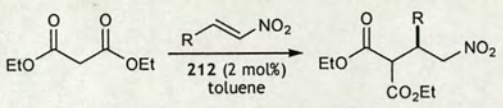


Table 6.4

Unfortunately, in the presence of substoichiometric quantities of a variety of chiral ligands only racemic products were obtained. Alternative magnesium salts such as $Mg(OTf)_2$ also gave racemic products. From these results it would appear that either magnesium is not involved in the stereochemical-determining step or that there is inefficient magnesium-ligand complexation. A this stage we elected to investigate the use of a chiral non-racemic Ni(II) complex as a potential catalyst in the transformation. As previously illustrated, $Ni(acac)_2$ proved to be ineffective as a catalyst in the cyclisation, even in the presence of K_2CO_3 (Table 6.1, entry 10). Nevertheless, such Ni(II) complexes have been shown to promote the enantioselective intermolecular Michael addition of a variety of malonates to several nitro-olefins (Table 6.5).[91]



R	%Yield	%ee
4-MeOPh	99	95
2,3-(MeO)Ph	99	93
2-furyl	98	95
4-MePh	99	95
4-ClPh	98	92
$CH(Me)_2$	82	90

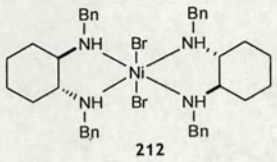
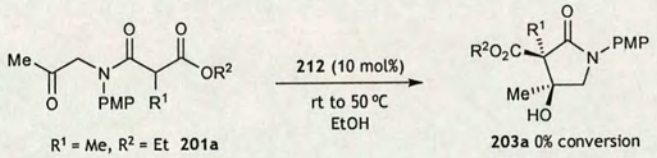


Table 6.5

In the event, no cyclisation was observed in the presence of the nickel salt, even at elevated temperatures (eq 53 and 54). The use of alternative solvents such as toluene, CH_2CCl_2 and THF also resulted in negligible reactivity.



R^1 = Me, R^2 = Et **201a**
R^1 = Ph, R^2 = ^{t}Bu **201d**

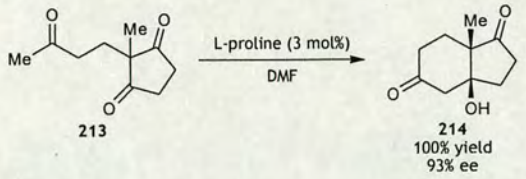
203a 0% conversion (53)
203d 0% conversion (54)

In conclusion, it has been shown that the use of Lewis acid-catalysis results in minimal substrate scope and to date no asymmetric induction has been observed. As a consequence it was necessary to consider alternative catalyst systems that would allow the cyclisation of a broader range of substrates with observable enantiomeric excesses.

6.1.2. Organocatalyst mediated cyclisations

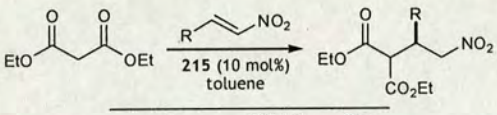
The development of organocatalysts has become a significant area of interest that has provoked enormous amounts of research into the discovery of new organic molecules that catalyse reactions only previously mediated by metal-ligand combinations. In this respect, we considered the use of known organocatalysts as potential mediators in the aldol cyclisation of malonate substrates **201**. Most notably, (L)-proline has proven to be a potent and highly stereoselective promoter for the aldol cyclisation of

trione **213** in the Hajos-Parrish-Eder-Sauer-Wiechert reaction, to produce bicyclic product **214** in excellent yield (eq 55).[92]

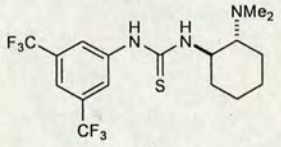


213 **214** 100% yield 93% ee (55)

Despite this isolated example other aldol cyclisations are rare in the chemical literature. However, in related areas the development of efficient catalyst systems has continued to advance and break new ground. For example, the conjugate addition of diethylmalonate into a variety of nitroolefins catalysed by the bifunctional organocatalyst species **215** offers some insight into the applicability of our hypothesis (Table 6.6).[93]



R	%Yield	%ee
Ph	86	93
2,6-$(MeO)_2$Ph	87	93
4-FPh	87	92
2-thienyl	74	90
pentyl	78	81
^{t}Bu	88	81



215

Table 6.6

Therefore, we focused on screening several bifunctional organic molecules as potential catalysts in our aldol cyclisation. From the outset cinchona alkaloids were considered as their use as organo-catalytic reagents has been well documented.[94, 95] These catalysts are likely to operate *via* duel activation of the substrate molecule (Figure 6.1). Firstly, the tertiary amine moiety serves to activate the nucleophile by the deprotonation of the malonate unit resulting in a tight ion-pair, the efficiency of which will greatly depend on the *pKa* of the malonate proton. Secondly, the pendant alcohol substituent acts as a hydrogen-bond donor, coordinating with the acceptor

ketone and increasing its inherent electrophilicity. The degree of ketone activation by the hydroxy-group will depend upon its hydrogen-bond-donating ability; a stronger donating-ability will result in greater activation

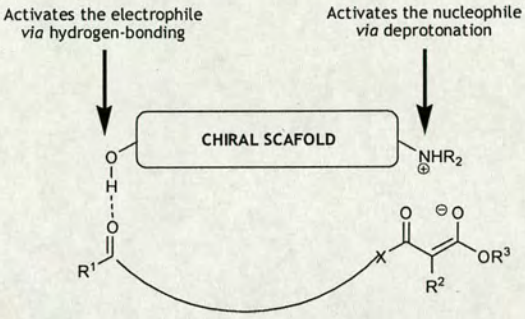
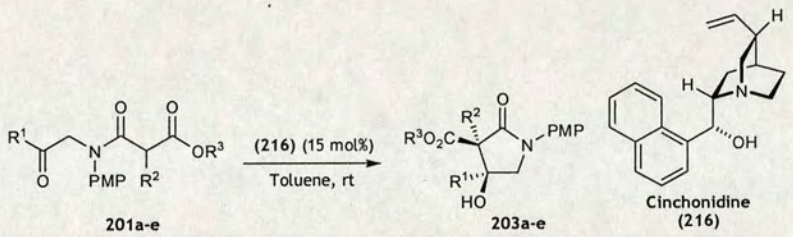
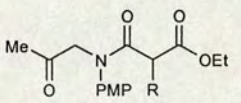
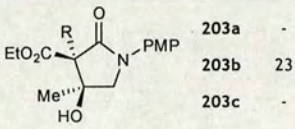
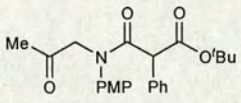
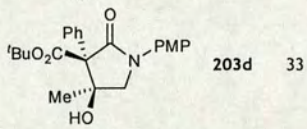
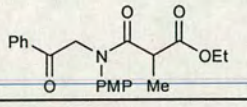
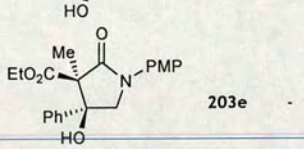


Figure 6.1

Initially, cinchonidine **(216)** was tested for catalytic activity against a number of substrates (Table 6.7).



Entry	Substrate		Product		ee%	%Conversion[a]
1		R = Me **201a**		**203a**	-	<5
2		R = Ph **201b**		**203b**	23	60
3		R = Bn **201c**		**203c**	-	<5
4		**201d**		**203d**	33	60
5		**201e**		**203e**	-	<5

[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures

Table 6.7

Similarly to the results described for the magnesium-catalysed cyclisation of substrates **201** (Table 6.2), the incorporation an aryl ketone results in negligible reactivity (entry 5). Additionally, substrates containing an alkyl substituted malonate unit (entries 1 and 3) are also poor substrates. This is most likely due to insufficient substrate activation and deprotonation by the weakly basic catalyst. It should be noted that ester tethered substrates; such as those described previously (Table 6.3) are also unreactive under these conditions. The only substrates that result in product formation are **201b** and **201d** giving the desired β-hydroxylactams **203b** and **203d** respectively in 60% conversion and with diastereoselectivities of >19:1(entries 2 and 4). The apparent reactivity of these substrates is almost certainly due to the sp^2-hydridised phenyl substituent on the malonate component increasing the acidity of the malonate proton, hence, allowing its deprotonation by the weakly basic cinchonidine catalyst. Gratifyingly, the analysis of the reaction mixtures by chiral HPLC indicated that products **203b** and **203d** had formed with an enantiomeric excess of 23% and 33% respectively. As a consequence, alternative amino-alcohol derivatives were screened for reactivity and asymmetric induction in the cyclisation of substrate **203d** (Table 6.8).

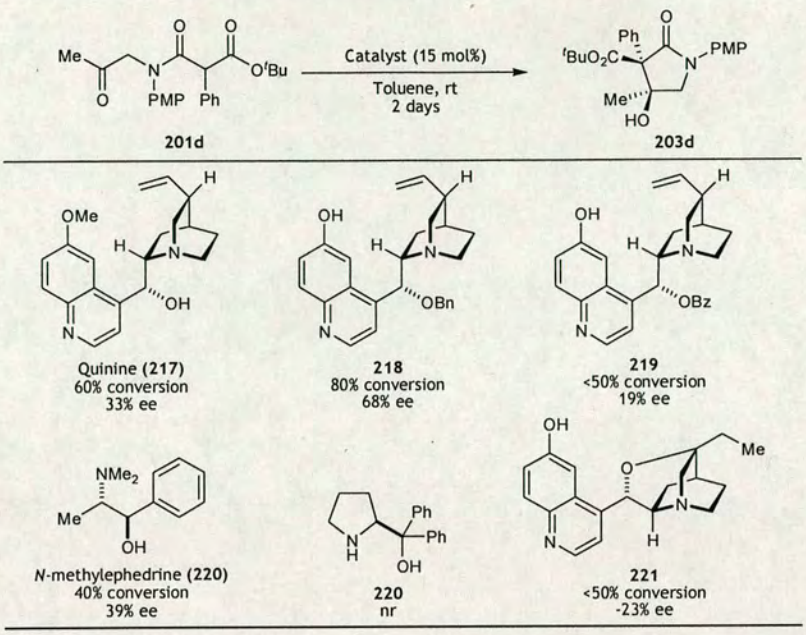
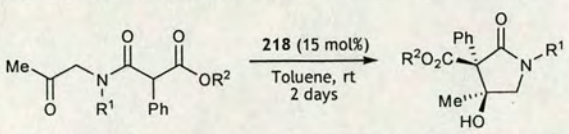


Table 6.8

The majority of amino-alcohol derivates tested result in poor reactivity and/or poor selectivity. However, use of modified quinine derivative **218** resulted in 80% conversion of starting material, producing the aldol product **201d** in an impressive 68% enantiomeric excess and with a diastereomeric ratio of >19:1.

Additionally, it was perceived that the pendant ester substituent would have an effect on the selectivity of the process. Therefore, a variety of ester substituents were examined (Table 6.9).



Entry	R^1	R^2	Product	%Conversion[a]	%ee[b]
1	PMP	Et **201b**	**203b**	95	47
2	PMP	^{i}Pr **222a**	**223a**	95	63
3	PMP	^{t}Bu **201d**	**203d**	95	68
4	PMP	^{t}Amyl **222b**	**223b**	95	63
5	Bn	^{t}Bu **222c**	**223c**	100	65

[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures
[b]Determined by chiral HPLC analysis of the unpurified reaction mixtures

Table 6.9

In all cases the reactions proceed well giving the desired products in >95% conversion and with diastereoselectivities of >19:1. As suggested the ester substituent does indeed influence the stereochemical outcome of the reaction. Substrate **201b** incorporating an ethyl ester provides the product in an unimpressive 47% ee (entry 1). Increasing the steric bulk of the ester also results in an increase in the enantiomeric excess with substrates **222a** and **201d** incorporating *iso*-propyl and *tert*-butyl substituents respectively, providing the products with the highest levels of stereoselection (entries 2 and 3). By increasing the steric bulk of the ester group further **222b**, results in a decrease in the selectivity (entry 4). The replacement of the electron-rich PMP protecting group with the more electron-neutral benzyl group **222c** results in an augmented reaction rate with little effect on the diastereo- or enantioselectivity (entry 5).

Furthermore, the relative stereochemistry of the major diastereomer of lactam **223a** was confirmed by X-ray crystallography (Figure 6.2).

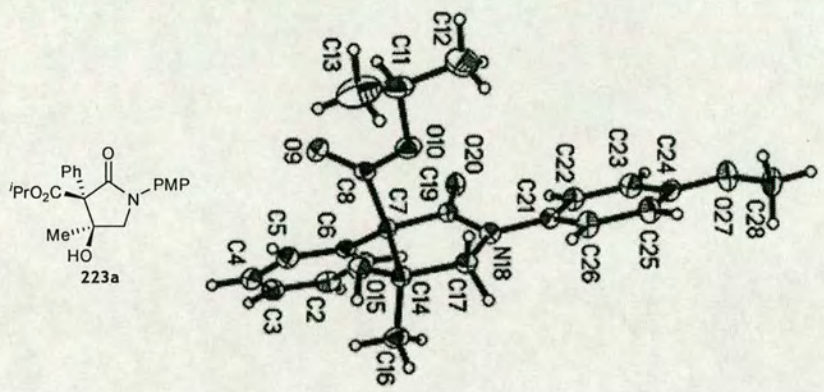
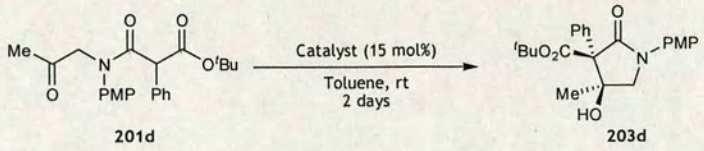
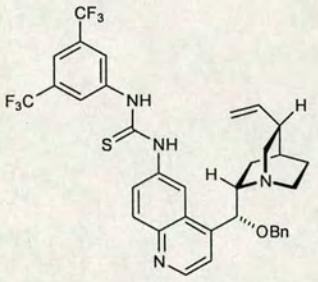


Figure 6.2

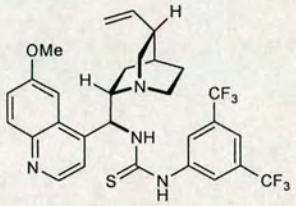
As previously stated the catalysts operate through a duel activation of the substrate molecule, with the tertiary amine functionality activating the nucleophile through deprotonation (Figure 6.1). In order to increase substrate activation by the catalyst it is necessary to augment its hydrogen-bond-donating ability. In this regard, Jacobsen,[96] Takemoto[93] and Connon[97] have pioneered the use of chiral thiourea derivatives as powerful hydrogen-bond-donor catalysts that promote a diverse range of reactions with excellent enantioselectivity. Therefore, the replacement of the donor-hydroxy group with a thiourea moiety should, in principle result in greater catalyst activity. To explore these effects two thiourea catalysts **224** and **225** were evaluated for efficacy (eq 56).



201d 203d (56)



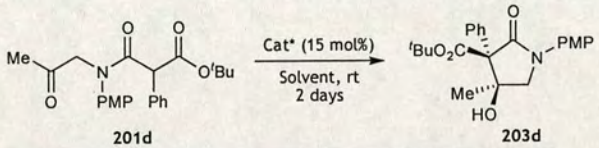
224
90% conversion
42% ee



225
100% conversion
16% ee

Although the use of the thiourea catalysts **224** and **225** gave increased conversion of starting material, the enantioselectivities were inferior to that obtained for quinine derivative **218**.

In an effort to increase the selectivity of the process a number of relatively non-polar, aprotic solvents were investigated and in the presence of a variety of catalysts, the conversion and selectivities were evaluated with the most promising results detailed below (Table 6.10).



201d 203d

Entry	Solevnt	Catalyst	%Conversion[a]	%ee[b]
1	Toluene	**218**	*ca.* 90	68
2	EtOAc	**218**	*ca.* 90	70
3	Et_2O	**218**	*ca.* 40	71
4	THF	**218**	*ca.* 95	70
5	Dioxane	**218**	*ca.* 95	71
6	EtOAc	**224**	*ca.* 90	63
7	Et_2O	**224**	*ca.* 40	77

[a]Determined by ^{1}H NMR analysis of the unpurified reaction mixtures
[b]Determined by chiral HPLC analysis of the unpurified reacrion mixtures

Table 6.10

The choice of solvent was observed to effect both the conversion and the enantioselectivity in the formation of **201d**. In the presence of **218** as the catalyst, the use of Et_2O as solvent gives the aldol product in 71% ee; however, due to the poor solubility of **218** in Et_2O the conversion was limited to 40% (entry 3). This could be overcome by replacing Et_2O with 1,4-dioxane as the solvent, giving the aldol product in 95% conversion and with 71% enantiomeric excess (entry 3). Likewise, the use of EtOAc and THF gives high levels of conversion with similar levels of selection (entries 4 and 5). In the presence of **224** as the catalyst, the use of toluene was noted to offer high conversion levels but with poor enantioselectivities (eq 56). However, the replacement of toluene with Et_2O allowed the aldol product to be generated in 77% ee, albeit with a greatly reduced conversion of 40% (entry 7) due to the poor solubility of the catalyst in Et_2O. By using EtOAc as the solvent the conversion levels could be increased; however, this resulted in a reduction in the enantioselectivity compared that obtained when Et_2O is used as solvent (entry 6). Alternative solvents such as CH_2Cl_2, $CHCl_3$, EtOH and DMSO were inferior to those described (Table 6.10). Notably, the diastereoselectivity of the process was not affected by the change in solvent.

6.2. *Conclusions and Further Work*

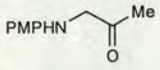
It has been demonstrated that a combination of substoichiometric quantities of $Mg(ClO_4)_2$ and K_2CO_3 effects the aldol cyclisation of substituted malonate moieties tethered to a methyl ketone *via* an amide linkage. However, the substrate scope is limited to a select group of amide tethered substrates such as **201b** and **201d**. Furthermore, ester linked substrates are not reactive under these conditions (Table 6.3). Subsquent attempts to render the magnesium-catalysed process enantioselective through the addition of chiral non-racemic ligands failed to yield any observable levels of selection. Further to this it has been illustrated that in the presence of modified cinchona alkaloids such as, **218** the aldol products could be obtained in >90% conversion and with enantioselectivities of up to 68%. Through modifications to the catalyst structure and a survey of reaction solvent conditions the levels of enantioselection could be further enhanced to a maximum of 77%. Nevertheless, the substrate scope in this area remains limited to the cyclisation of amide tethered

substrates bearing an sp^2-substituted malonate unit. Potential future work in this area would aim to identify more effective catalyst systems that will enable the cyclisation of a variety of substrates to occur with enantioselectivities of >90%. These may include other modified alkaloid derivatives or other bifunctional organocatalysts reported in the literature.

6.3. Experimental

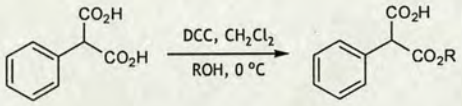
All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 was distilled from CaH_2. THF was distilled from sodium benzophenone ketyl. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40-60 °C. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate, ceric ammonium molybdate solution or vanillin solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.[80] Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^1H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm, $C_2D_2Cl_4$ at 5.94 ppm, CD_3OD at 3.35 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm, $C_2D_2Cl_4$ at 74.2 ppm, CD_3OD at 49.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound. Chiral HPLC

analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

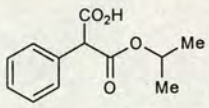


1-(4-Methoxyphenyl)aminopropanone (126). Prepared according to a previously reported procedure (Chapter 3.3).

Preparation of mono-esters from phenyl malonic acid: General Procedure P

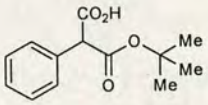


A DCC (1 equiv) solution in CH_2Cl_2 (50 mL) was added dropwise over 1 hour to a stirred solution of phenylmalonic acid (1 equiv) and the appropriate alcohol (1 equiv) in CH_2Cl_2 (150 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and the precipitated dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and partitioned between Et_2O (100 mL) and $NaHCO_{3(aq)}$ (100 mL). The aqueous layer was removed and washed with Et_2O (2 x 50 mL) then acidified to pH 3 by the addition of 2M $HCl_{(aq)}$. The aqueous layer was then extracted with EtOAc(3 x 50 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the corresponding mono-ester substituted phenylmalonic acid.

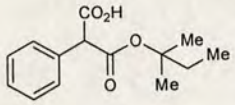


2-(isopropoxycarbonyl)-2-phenylacetic acid (226). The title compound was prepared according to general procedure P from phenylmalonic acid (11 g, 60 mmol), isopropanol (4.6 mL, 60 mmol) and DCC (12.4 g, 60 mmol) for a reaction time of 2 hrs. The product was obtained as a white solid (10.6 g, 80%). m.p. 68-70 °C; IR ($CHCl_3$) 3034 (OH), 2984, 1716 (C=O), 1498, 1304, 1167, 1033, 991, 815, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 11.5 (1H, bs, $CO_2\mathbf{H}$), 7.45-7.30 (5H, m, Ar**H**), 5.11 (1H, heptet, J = 6.3 Hz, OC**H**$(CH_3)_2$), 4.65 (1H, s, PhC**H**$(CO_2H)(CO_2R)$), 1.29 (3H, d, J = 6.3 Hz, OCH$(C\mathbf{H}_3)_2$), 1.24 (3H, d, J = 6.3 Hz, OCH$(C\mathbf{H}_3)_2$); ^{13}C NMR 178.3 (C), 174.0 (C), 167.6 (C), 129.1 (2 x CH), 128.7 (2 x CH), 128.7 (CH), 70.0 (CH), 57.7 (CH), 21.4

(CH_3), 21.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{12}H_{14}O_4$ $[M+NH_4]^+$: 222.0887, found: 222.0886.

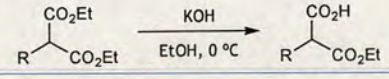


2-(*tert*-butoxycarbonyl)-2-phenylacetic acid (227). The title compound was prepared according to general procedure P from phenylmalonic acid (11 g, 60 mmol), *tert*-butanol (5.8 mL, 60 mmol) and DCC (12.4 g, 60 mmol) for a reaction time of 2 hrs. The product was isolated as a white solid (9.9 g, 70%). m.p. 72-73 °C; IR ($CHCl_3$) 2978 (OH), 1714 (C=O), 1498, 1370, 1145, 1032, 838, 750, 699, 668 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 11.80 (1H, s, O**H**), 7.44-7.30 (5H, m, Ar**H**), 4.60 (1H, s, PhC**H**($CO_2R)_2$), 1.49 (9H, s, C($C\mathbf{H}_3)_3$); ^{13}C NMR 178. 2 (C), 174.1 (C), 167.3 (C), 129.1 (2 x CH), 128.6 (2 x CH), 128.3 (CH), 83.0 (C), 58.5 (CH), 27.7 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{16}O_4$ $[M+NH_4]^+$: 236.1044, found: 236.1043.



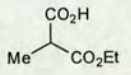
2-((*tert*-pentyloxy)carbonyl)-2-phenylacetic acid (228). The title compound was prepared according to general procedure P from phenylmalonic acid (11 g, 60 mmol), amylalcohol (60 mmol) and DCC (12.4 g, 60 mmol) for a reaction time of 2 hrs. The product was isolated as a white oil (8.7 g, 58%). IR ($CHCl_3$) 3033 (OH), 2978, 1713 (C=O), 1456, 1387, 1289, 1145, 1032, 830, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 11.73 (1H, bs, O**H**), 7.47-7.34 (5H, m, Ar**H**), 4.64 (1H, s, PhC**H**($CO_2R)_2$), 1.80 (2H, q, J = 7.5 Hz, $C\mathbf{H}_2CH_3$), 1.48 (6H, d, J = 2.9 Hz, $C(C\mathbf{H}_3)_2CH_2CH_3$), 0.87 (3H, t, J = 7.5 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR 178.1 (C), 174.1 (C), 167.1 (C), 129.1 (2 x CH), 128.7 (2 x CH), 128.5 (CH), 85.4 (C), 58.6 (CH), 33.4 (CH_2), 25.1 (CH_3), 25.1 (CH_3), 7.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{18}O_4$ $[M+NH_4]^+$: 250.1198, found: 250.1200.

Preparation of mono-ethyl-phenylmalonic acid: General Procedure Q

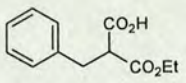


A potassium hydroxide (1 equiv) solution in ethanol (50 mL) was added dropwise over 1 hour to a stirred solution of the appropriate diethylmalonate (1 equiv) in

ethanol (90 mL) at 0 oC. The mixture was allowed to warm to room temperature and stirred until TLC analysis showed the reaction to be complete (*ca.* 2 days). The slightly turbid solution was heated to reflux and filtered through a glass sinter. After cooling to room temperature the solvent was removed under reduced pressure and the resultant white solid dissolved in H_2O (100 mL) and washed with Et_2O (3 x 30 mL). The aqueous layer was acidified with conc. HCl, extracted with EtOAc (3 x 30 mL), dried over $MgSO_4$ and concentrated under reduced pressure to yield the corresponding mono-ester substituted malonic acid.

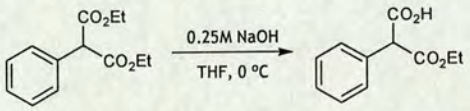


2-(ethoxycarbonyl)-2-methylacetic acid (229). The title compound was prepared according to general procedure Q from diethylmethylmalonate (17.2 mL, 100 mmol), potassium hydroxide (5.6 g, 100 mmol) for a reaction time of 2 days. The product was isolated as a colourless liquid (11.9 g, 82%). Analytical data corresponds to that reported.[98]



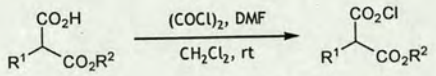
2-(ethoxycarbonyl)-3-phenylpropanoic acid (230). The title compound was prepared according to general procedure Q from diethylbenzylmalonate (12 mL, 50 mmol), potassium hydroxide (2.8 g, 50 mmol) for a reaction time of 2 days. The product was isolated as a colourless liquid (9.5 g, 86%). Analytical data corresponds to that reported.[99]

2-(ethoxycarbonyl)-2-phenylacetic acid (231).



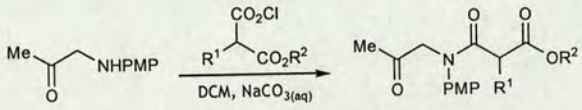
A solution of diethylphenylmalonate (11 mL, 50 mmol) in THF (100 mL) was added portionwise 0.25M $NaOH_{(aq)}$ (1.2 L) at 0 °C until TLC analysis showed the reaction to be complete (*ca.* 4 hrs). The mixture was washed with EtOAc (3 x 40 mL) and the combined organics were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was triturated with hot petrol/CH_2Cl_2 (50 mL) to give the product as a white solid (10.2 g, 98%). Analytical data corresponds to that reported.[100]

Preparation of Acid Chlorides: General Procedure R

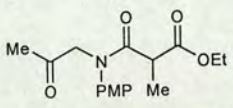


Oxalyl chloride (1.10 equiv) was added dropwise over 2 min to a solution of the appropriate mono-ester acid (1.00 equiv) and DMF (0.25 equiv) in CH_2Cl_2 (0.55 M with respect to carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h) to give a solution of mono-ester acid chloride which was used directly in the next step.

Preparation of Amide-Tethered Cyclisation Precursors: General Procedure S

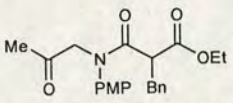


The appropriate mono-ester acid chloride (as a solution in CH_2Cl_2 prepared according to General Procedure R, 1.5 equiv) was added dropwise or portionwise to a vigorously stirred mixture of the appropriate aminoketone (1.0 equiv) in CH_2Cl_2 (1 mL/mmol of aminoketone) and saturated aqueous Na_2CO_3 solution (1 mL/mmol of aminoketone). The mixture was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2 (x 3), and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography afforded the cyclization substrate.

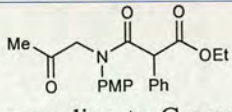


Ethyl-2-(N-(4-methoxyphenyl)-N-(2-oxopropyl)carbamyl)propanoate (201a). The title compound was prepared according to General Procedure S from the amine **126** (890 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure R) derived from 2-(ethoxycarbonyl)-2-methylacetic acid **229** (1.10 g, 7.50 mmol) for a reaction time of 30 mins and purified by column chromatography (30%

EtOAc/petrol) to give an orange oil (760 mg, 50%). IR ($CHCl_3$) 2984, 1739 (C=O), 1661, 1512, 1418, 1250, 1170, 1053, 1031, 845 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.04 (2H,d, J = 8.9 Hz, Ar**H**), 6.64 (2H, d, J = 8.9 Hz, Ar**H**), 4.27 (1H, d, J = 17.5 Hz, C**H**$_2$N), 4.01 (1H, d, J = 17.5 Hz, C**H**$_2$N), 3.78 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 3.52 (3H, s, OC**H**$_3$), 3.21 (1H, q, J = 7.1 Hz, CH$_3$C**H**(CO$_2$R)$_2$), 1.86 (3H, s, C**H**$_3$=O), 0.98 (3H, d, J = 7.1 Hz, C**H**$_3$CH(CO$_2$R)$_2$), 0.94 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 201.4 (C), 169.6 (C), 158.6 (C), 134.5 (C), 128.6 (2 x CH), 114.0 (2 x CH), 60.1 (CH_2), 58.8 (CH_3), 54.6 (CH), 42.3 (CH_2), 26.2 (CH_3), 13.2 (CH_3), 13.1 (CH_3) ; HRMS (ES) Exact mass calcd for $C_{16}H_{21}NO_5$ $[M+H]^+$: 307.1417, found: 307.1414.

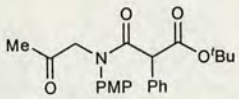


Ethyl-2-(*N*-(4-methoxyphenyl)-*N*-(2-oxopropyl)carbamoyl)-3-phenylpropanoate (201c). The title compound was prepared according to General Procedure S from the amine **126** (890 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure R) derived from 2-(ethoxycarbonyl)-3-phenylpropanoic acid **230** (1.60 g, 7.50 mmol) for a reaction time of 2 hrs and purified by column chromatography (30% Et_2O/Petrol) to give a caramel oil (1.68 g, 90%). IR ($CHCl_3$) 2980, 1739 (C=O), 1660, 1512, 1251, 1170, 1030, 843, 755, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.19-7.13 (3H, m, Ar**H**), 6.96 (2H, d, J = 7.6 Hz, Ar**H**), 6.76-6.67 (2H,m, Ar**H**), 4.27 (1H, d, J = 17.3 Hz, C**H**$_2$N), 4.12 (1H, d, J = 17.3 Hz, C**H**$_2$N), 4.02 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 3.67 (3H, s, OC**H**$_3$), 3.56 (1H, dd, J = 9.5, 5.5 Hz, C**H**(CO$_2$R)$_2$), 3.10 (1H, dd, J = 13.5, 9.5 Hz, PhC**H**$_2$CH), 3.00 (1H, dd, J = 13.5, 5.5 Hz, PhC**H**$_2$CH), 2.00 (3H, s, C**H**$_3$=O), 1.16 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 201.7 (C), 168.7 (C), 168.6 (C), 158.8 (C), 137.9 (C), 134.3 (C), 129.1 (2 x CH), 128.8 (3 x CH), 127.9 (2 x CH), 126.1 (C), 114.1 (2 x CH), 60.8 (CH_2), 59.2 (CH_2), 55.0 (CH_3), 50.1 (CH), 34.6 (CH_2), 26.6 (CH_3), 13.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{25}NO_5$ $[M+H]^+$: 383.1727, found: 383.1723.

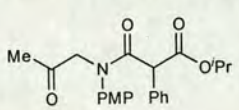


Ethyl-2-(*N*-(4-methoxyphenyl)-*N*-(2-oxopropyl)carbamyl)-2-phenylacetate (201b). The title compound was prepared according to General Procedure S from the amine **126** (890 mg, 5.00 mmol) and the

acid chloride (prepared according to General Procedure R) derived from 2-(ethoxycarbonyl)-2-phenylacetic acid **231** (1.56 g, 7.50 mmol) for a reaction time of 2 hrs and purified by column chromatography (30% Et_2O/Petrol) to give a light yellow solid (1.52 g, 83%). m.p. 67-69 °C. IR ($CHCl_3$) 2979, 1734 (C=O), 1659 (C=O), 1512, 1385, 1250, 1170, 1028, 841, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.26 (4H, m, Ar**H**), 7.17 (3H, m, Ar**H**), 6.86 (2H, bd, J = 8.1 Hz, Ar**H**), 4.68 (1H, s, C**H**$(CO_2R)_2$), 4.45 (1H, d, J = 17.4 Hz, C**H**$_2$N), 4.37 (1H, d, J = 17.4 Hz, C**H**$_2$N), 4.17 (2H, q, J = 7.1 Hz OC**H**$_2$CH$_3$), 3.83 (3H, s, OC**H**$_3$), 2.14 (3H, s, C**H**$_3$=O), 1.26 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 201.9 (C), 168.6 (C), 168.3 (C), 159.4 (C), 134.8 (C), 133.3 (C), 129.6 (2 x CH), 129.4 (2 x CH), 128.2 (2 x CH), 127.7 (CH), 114.7 (2 x CH), 61.5 (CH_2), 59.7 (CH_2), 55.4 (CH_3), 27.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{23}NO_5$ $[M+H]^+$: 369.1572, found: 396.1571.

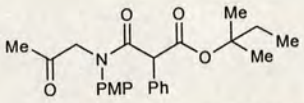


***tert*-butyl-2-(*N*-(4-methoxyphenyl)-*N*-(2-oxopropyl)carbamyl)-2-phenylacetate (201d).** The title compound was prepared according to General Procedure S from the amine **126** (890 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure R) derived from 2-(*tert*-butoxycarbonyl)-2-phenylacetic acid **227** (1.77 g, 7.50 mmol) for a reaction time of 4 hrs and purified by column chromatography (30% EtOAc/Petrol) to give a beige solid (1.05 g, 53%). m.p. 109 °C. IR ($CHCl_3$) 2977, 1738 (C=O), 1659, 1512, 1368, 1251, 1146, 1066, 1030, 840 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.32-7.26 (4H, m, Ar**H**), 7.21-7.19 (3H, m, Ar**H**), 6.90 (2H, bd, J = 8.2 Hz, Ar**H**), 4.62 (1H, s, PhC**H**$(CO_2R)_2$), 4.45 (1H, d, J = 17.5 Hz, C**H**$_2$N), 4.31 (1H, d, J = 17.5 Hz, C**H**$_2$N), 3.84 (3H, s, OC**H**$_3$), 2.14 (3H, s, C**H**$_3$=O), 1.49 (9H, s, O(C**H**$_3$)$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 201.7 (C), 168.4 (C), 167.5 (C), 159.2 (C), 134.9 (C), 133.5 (C), 129.5 (2 x CH), 129.3 (2 x CH), 127.9 (2 x CH), 127.4 (2 x CH), 81.6 (C), 59.5 (CH), 55.7 (CH_2), 55.3 (CH_3), 27.6 (3 x CH_3), 26.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{27}NO_5$ $[M+H]^+$: 388.1962, found: 398.1961.



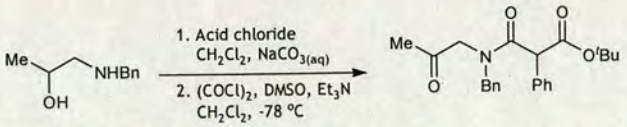
isopropyl-2-(*N*-(4-methoxyphenyl)-*N*-(2-oxopropyl)carbamyl)-2-phenylacetate (222a). The title

compound was prepared according to General Procedure S from the amine **126** (890 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure R) derived from 2-(isopropoxycarbonyl)-2-phenylacetic acid **226** (1.67 g, 7.50 mmol) for a reaction time of 4 hrs and purified by column chromatography (50% EtOAc/Petrol) to give a beige crystalline solid (1.08 g, 51%). m.p. 126-127 °C. IR ($CHCl_3$) 2980, 1737 (C=O), 1660, 1512, 1385, 1251, 1170, 1106, 1030, 843 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.26 (4H, m, Ar**H**), 7.19-7.16 (3H, m, Ar**H**), 6.88 (2H, bd, J = 8.5 Hz, Ar**H**), 5.02 (1H, septet, J = 6.1 Hz, C**H**$(CH_3)_2$), 4.65 (1H, s, PhC**H**$(CO_2R)_2$), 4.39 (2H, s, C**H**$_2$N), 3.84 (3H, s, OC**H**$_3$), 2.15 (3H, s, C**H**$_3$=O), 1.25 (6H, appt, J = 6.1 Hz, OCH$(CH_3)_2$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ; HRMS (ES) Exact mass calcd for $C_{22}H_{25}NO_5$ $[M+H]^+$: 384.1805, found: 384.1806.



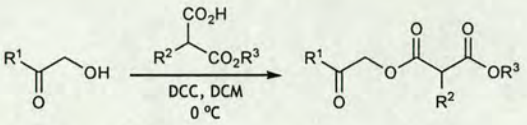
***tert*-pentyl-2-(*N*-(4-methoxyphenyl)-*N*-(2-oxopropyl)carbamyl)-2-phenylacetate (222b).** The title compound was prepared according to General Procedure S from the amine **126** (890 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure R) derived from 2-(*tert*-pentoxycarbonyl)-2-phenylacetic acid **228** (1.88 g, 7.50 mmol) for a reaction time of 4 hrs and purified by column chromatography (50% EtOAc/Petrol) to give a beige crystalline solid (1.21 g, 59%). m.p. 87-88 °C. IR ($CHCl_3$) 2975, 1739 (C=O), 1660, 1512, 1384, 1251, 1145, 1065, 1030, 841 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.29-7.26 (4H, m, Ar**H**), 7.20-7.18 (3H, m, Ar**H**), 6.89 (2H, bd, J = 8.4 Hz, Ar**H**), 4.61 (1H, s, PhC**H**$(CO_2R)_2$), 4.43 (1H, d, J = 17.4 Hz, C**H**$_2$N), 4.35 (1H, d, J = 17.4 Hz, C**H**$_2$N), 3.85 (3H, s, OC**H**$_3$), 2.15 (3H, s, C**H**$_3$=O), 1.78 (2H, q, J = 7.5 Hz, O$(CH_3)_2$C**H**$_2$$CH_3$), 1.45 (6H, s, O(C**H**$_3$$)_2CH_2CH_3$), 0.86 (3H, t, J = 7.5 Hz, O$(CH_3)_2CH_2$C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 201.9 (C), 168.6 (C), 167.6 (C), 159.3 (C), 135.0 (C), 133.6 (C), 129.6 (2 x CH), 129.4 (2 x CH), 128.0 (2 x CH), 127.5 (CH), 114.6 (2 x CH), 84.3 (C), 59.6 (CH_2), 55.9 (CH_3), 55.4 (CH), 33.5 (CH_2), 27.0 (CH_3), 25.2 (CH_3), 25.1 (CH_3) 8.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{24}H_{29}NO_5$ $[M+H]^+$: 412.2118, found: 412.2116.

tert-butyl-2-(_N_-benzyl-_N_-(2-oxopropyl)carbamyl)-2-phenylacetate (222c).

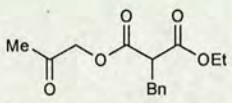


The title compound was prepared according to General Procedure S from 1-(benzylamino)propan-2-ol (890 mg, 5.00 mmol) and the acid chloride (prepared according to General Procedure R) derived from 2-(tert-butoxycarbonyl)-2-phenylacetic acid **227** (1.10 g, 7.50 mmol) for a reaction time of 8 hrs. The crude product was taken forward without further purification. A solution of oxalyl chloride (486 μL, 5.46 mmol) in CH_2Cl_2 (20 mL) was cooled to −78 °C then DMSO (776 μL, 10.92 mmol) was added and the mixture allowed to stir for 20 mins. A solution of the crude amide in CH_2Cl_2 (20 mL) was added *via* cannula and the mixture allowed to stir for 1 hour at −78 °C before Et_3N was added dropwise over 10 mins. The mixture was allowed to slowly warm to room temperature over 3 hrs then quenched by the addition of saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL) and the combined organics dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatograophy (30% Et2O/Petrol) to give a white solid. m.p. 95-97 °C; IR ($CHCl_3$) 2978, 1740 (C=O), 1653, 1497, 1431, 1367, 1150, 1031, 920, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.31 (9H, m, Ar**H**), 7.14-7.11 (1H, m, Ar**H**), 5.30 (1H, s, PhC**H**$(CO_2R)_2$), 4.64 (1H, d, J = 16.8 Hz, C**H**$_2$N), 4.45 (1H, d, J = 16.8 Hz, C**H**$_2$N), 4.25 (1H, d, J = 17.5 Hz, NC**H**$_2$Ph), 3.92 (1H, d, J = 17.5 Hz, NC**H**$_2$Ph), 2.09 (3H, s, C**H**$_3$=O), 1.49 (9H, s, C(C**H**$_3)_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 202.7 (C), 169.0 (C), 167.4 (C), 135.5 (C), 133.2 (C), 129.4 (CH), 128.9 (CH), 128.6 (CH), 128.0 (CH), 126.8 (CH), 82.2 (C), 56.6 (CH), 55.2 (CH_3), 52.4 (CH_2), 27.9 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{27}NO_4$ $[M+H]^+$: 381.1935, found: 381.1931.

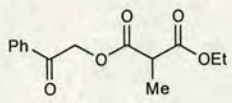
Preparation of Ester-Tethered Cyclisation Precursors: General Procedure T



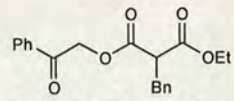
A DCC (1 equiv) solution in CH_2Cl_2 (5 mL) was added dropwise over 1 hour to a stirred solution of phenylmalonic acid (1 equiv) and the appropriate alcohol (1 equiv) in CH_2Cl_2 (5 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then allowed to warm to room temperature and the precipitated dicyclohexylurea was removed by filtration. The filtrate was concentrated under reduced pressure and partitioned between Et_2O (10 mL) and $NaHCO_3$(aq) (10 mL). The aqueous layer was removed and washed with Et_2O (2 x 20 mL) then acidified to pH 3 by the addition of concentrated HCl. The aqueous layer was then extracted with EtOAc(3 x 10 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to yield the corresponding ester-tethered cyclisation substrate.



1-ethyl-3-(2-oxopropyl)-2-benzylmalonate (205c). The title compound was prepared according to General Procedure T from hydroxyacetone (381 μL, 5.00 mmol) and the malonic acid **230** (prepared according to General Procedure R) (1.39 g, 5.00 mmol) and DCC (1.03 g, 5.00 mmol) for a reaction time of 4 hrs and purified by column chromatography (50% EtOAc/Petrol) to give a colourless oil (904 mg, x%). IR ($CHCl_3$) 2983, 1734 (C=O), 1455, 1370, 1279, 1226, 1147, 1064, 753, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.27 (2H, m, Ar**H**), 7.24-7.21 (3H, m, Ar**H**), 5.19 (2H, s, C**H**$_2$O), 4.87 (2H, q, J = 5.6 Hz, $CH_3C\mathbf{H}_2O$), 4.53 (1H, t, J = 6.2 Hz, C**H**$(CO_2R)_2$), 4.12 (2H, d, J = 6.2 Hz, Ar**CH**$_2$), 3.18 (3H, s, C**H**$_3$=O), 2.49 (3H, t, J = 5.6 Hz, C**H**$_3$CH$_2$O); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 201.1 (C), 168.3 (C), 168.2 (C), 137.5 (C), 128.8 (2 x CH), 128.5 (2 x CH), 126.8 (CH), 68.9 (CH_2), 61.7 (CH_2), 53.4 (CH), 34.6 (CH_2), 25.9 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{18}O_5$ $[M+H]^+$: 278.1149, found: 278.1152.

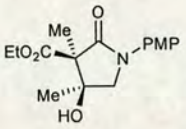


1-ethyl-3-(2-oxo-1-phenylethanone)-2-methylmalonate (205a). The title compound was prepared according to General Procedure T from 2-hydroxyacetophenone (680 mg, 5.00 mmol) and the malonic acid **229** (prepared according to General Procedure R) (1.04 g, 5.00 mmol) and DCC (1.03 g, 5.00 mmol) for a reaction time of 6 hrs and purified by column chromatography (20% EtOAc/Petrol) to give a yellow oil (995 mg, 75%). IR ($CHCl_3$) 2988, 1755 (C=O), 1733 (C=O), 1705 (C=O), 1450, 1371, 1332, 1224, 1096, 863 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.91-7.88 (2H, m, Ar**H**), 7.63-7.58 (1H, m, Ar**H**), 7.51-7.46 (2H, m, Ar**H**), 5.44 (1H, d, J = 16.3 Hz, C**H**$_2$O), 5.33 (1H, d, J = 16.3 Hz, C**H**$_2$O), 4.23 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 3.64 (1H, q, J = 7.3 Hz, CH$_3$C**H**(CO$_2$R)$_2$), 1.52 (3H, d, J = 7.3 Hz, C**H**$_3$CH(CO$_2$R)$_2$); 1.29 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 191.4 (C), 169.7 (C), 169.6 (C), 134.0 (C), 133.9 (2 x CH), 128.8 (4 x CH), 127.7 (4 x CH), 66.5 (CH_2), 61.5 (CH_2), 45.9 (CH), 14.0 (CH_3), 13.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{16}O_5$ $[M+H]^+$: 264.0992, found: 264.0992.

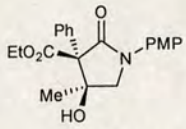


1-ethyl-3-(2-oxo-1-phenylethanone)-2-benzylmalonate (205b). The title compound was prepared according to General Procedure T from 2-hydroxyacetophenone (680 mg, 5.00 mmol) and the malonic acid **231** (prepared according to General Procedure R) (1.06 g, 5.00 mmol) and DCC (1.03 g, 5.00 mmol) for a reaction time of 6 hrs and purified by column chromatography (20% EtOAc/Petrol) to give a yellow oil (1.03 g, 62%). IR ($CHCl_3$) 2982, 1755 (C=O), 1735 (C=O), 1705 (C=O), 1450, 1370, 1284, 1223, 1148, 754 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.88 (2H, d, J = 8.5 Hz, Ar**H**), 7.60 (1H, tt, J = 7.5, 7.5, 1.3, 1.3 Hz, Ar**H**),7.48 (2H, tq, J = 7.5 Hz, Ar**H**), 7.32-7.20 (5H, m, Ar**H**), 5.36 (2H, d, J = 3.6 Hz, C**H**$_2$O), 4.18 (2H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 3.87 (1H, t, J = 7.8 Hz, C**H**(CO$_2$R)$_2$), 3.34 (2H, dd, J = 7.8, 2.1 Hz, ArC**H**$_2$), 1.21 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 191.2 (C), 168.4 (C), 168.3 (C), 137.7 (C), 133.9 (C), 128.8 (6 x CH), 128.5 (2 x CH), 127.7 (2 x CH), 126.7 (C), 66.6 (CH_2), 61.6 (CH_2), 53.5 (CH), 34.6 (CH_2) 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{20}H_{20}O_5$ $[M+H]^+$: 340.1305, found: 340.1308.

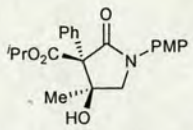
Transition-Metal Catalysed Cyclisations: General Procedure U



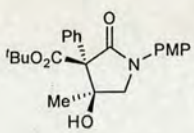
(3*S*,4*R*)-ethyl-4-hydroxy-1-(4-methoxyphenyl)-3,4-dimethyl-2-oxopyrrolidine-3-carboxylate (203a). The title compound was prepared according to general procedure U from precursor **201a** and isolated as a 2:1 mixture of diastereomers yellow oil. IR ($CHCl_3$) 3441, 2959, 1742 (C=O), 1697, 1510, 1395, 1287, 1250, 1031, 833, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.48 (2H, d, J = 9.2 Hz, Ar**H**), 6.92 (2H, D, J = 9.2 Hz, Ar**H**), 4.32-4.11 (2H, m, C**H**$_2$CH$_3$), 4.00 (1H, d, J = 10.0 Hz, C**H**$_2$N, *major*), 3.90 (1H, d, J = 9.7 Hz, C**H**$_2$N, *minor*), 3.81 (3H, s, OC**H**$_3$), 3.68 (1H, d, J = 10.0 Hz, C**H**$_2$N, *major*), 3.64 (1H, d, J = 9.7 Hz, C**H**$_2$N, *minor*), 1.47 (3H, s, C**H**$_3$, *major*), 1.43 (3H, s, C**H**$_3$, *minor*), 1.38 (3H, s, C**H**$_3$), 1.31 (3H, t, J = 7.1 Hz, CH$_2$C**H**$_3$, *minor*), 1.26 (3H, t, J = 7.1 Hz, CH$_2$C**H**$_3$, *major*); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ ; HRMS (ES) Exact mass calcd for $C_{16}H_{21}NO_5$ $[M+H]^+$: 307.1414, found: 307.1420.



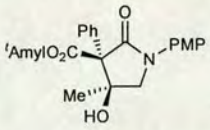
(3*S*,4*R*)-ethyl-4-hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxo-3-phenylpyrrolidine-3-carboxylate (201b). The title compound was prepared according to general procedure U from precursor **203b** and isolated as a yellowish oil. IR ($CHCl_3$) 3445, 2963, 1747 (C=O), 1697,1513, 1398, 1290, 1252, 1035, 831, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59 (2H, d, J = 9.2 Hz, Ar**H**), 7.37-7.32 (5H, m, Ar**H**), 6.95 (2H, D, J = 9.2 Hz, Ar**H**), 5.15 (1H, bs, O**H**), 4.30 (2H, qq, J = 10.6, 7.1 Hz, OC**H**$_2$CH$_3$), 3.91 (1H, d, J = 9.6 Hz, C**H**$_2$N), 3.82 (3H, s, OC**H**$_3$), 3.59 (1H, d, J= 9.6 Hz, C**H**$_2$N), 1.28 (3H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$), 1.11 (3H, s, C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 171.5 (C), 167.0 (C), 157.0 (C), 134.8 (C), 132.0 (C), 128.5 (2 x CH), 127.9 (3 x CH), 122.1 (2 x CH), 114.1 (2 x CH), 76.4 (C), 67.8 (C), 62.5 (CH_2), 58.8 (CH_2), 55.4 (CH_3), 24.1 (CH_3), 13.7 (CH), 0.95 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{23}NO_5$ $[M+H]^+$: 369.1571, found: 369.1569. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 14.0 min, t_r (major) = 18.4 min.



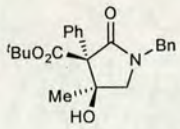
(3*S*,4*R*)-isopropyl-4-hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxo-3-phenylpyrrolidine-3-carboxylate (223a). The title compound was prepared according to general procedure U from precursor **222a** and isolated as a white solid. m.p. 118-120 °C; IR ($CHCl_3$) 3444, 2980, 1743 (C=O), 1693, 1513, 1375, 1288, 1250, 1035, 831, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59 (2H, d, *J* = 9.2 Hz, Ar**H**), 7.37-7.31 (5H, m, Ar**H**), 6.95 (2H, D, *J* = 9.2 Hz, Ar**H**), 5.23 (1H, bs, O**H**), 5.18 (1H, septet, *J* = 6.3 Hz, OC**H**$(CH_3)_2$), 3.90 (1H, d, *J* = 9.6 Hz, C**H**$_2$N), 3.82 (3H, s, OC**H**$_3$), 3.58 (1H, d, *J* = 9.6 Hz, C**H**$_2$N), 1.25 (3H, d, *J* = 6.3 Hz, OCH(C**H**$_3)_2$), 1.19 (3H, d, *J* = 6.3 Hz, OCH(C**H**$_3)_2$), 1.10 (3H, s, C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 171.1 (C), 167.1 (C), 157.0 (C), 135.0 (C), 132.1 (C), 128.4 (2 x CH), 128.0 (2 x CH), 127.7 (CH), 122.2 (2 x CH), 114.2 (2 x CH), 70.5 (CH), 67.8 (C), 58.9 (CH_2), 55.5 (CH_3), 24.2 (CH_3), 21.4 (CH_3), 21.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{22}H_{25}NO_5$ $[M+H]^+$: 383.1727, found: 383.1726. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 19.9 min, t_r (major) = 17.6 min.



(3*S*,4*R*)-*tert*-butyl-4-hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxo-3-phenylpyrrolidine-3-carboxylate (223d). The title compound was prepared according to general procedure U from precursor **222d** and isolated as a white solid. m.p. 169-170 °C; IR ($CHCl_3$) 3435, 2976, 1744 (C=O), 1691, 1513, 1368, 1291, 1251, 1034, 831, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 9.2 Hz, Ar**H**), 7.42-7.31 (5H, m, Ar**H**), 6.95 (2H, d, *J* = 9.2 Hz, Ar**H**), 5.28 (1H, bs, O**H**), 3.89 (1H, d, *J* = 9.5 Hz, C**H**$_2$N), 3.83 (3H, s, OC**H**$_3$), 3.57 (1H, d, *J* = 9.5 Hz, C**H**$_2$N), 1.44 (9H, s, OC(C**H**$_3)_3$), 1.10 (3H, s, C**H**$_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 170.6 (C), 167.4 (C), 157.0 (C), 135.3 (C), 128.3 (2 x CH), 128.0 (2 x CH), 127.6 (CH), 122.2 (2 x CH), 114.2 (2 x CH), 84.1 (C), 68.0 (C), 59.0 (CH_2), 55.5 (CH_3), 27.7 (3 x CH_3), 24.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{23}H_{27}NO_5$ $[M+H]^+$: 397.1884, found: 397.1883. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 17.1 min, t_r (major) = 15.7 min.



(3*S*,4*R*)-*tert*-pentyl-4-hydroxy-1-(4-methoxyphenyl)-4-methyl-2-oxo-3-phenylpyrrolidine-3-carboxylate (223b). The title compound was prepared according to general procedure U from precursor **222b** and isolated as a white solid. m.p. 149-151 °C; IR ($CHCl_3$) 3435, 2975, 1742 (C=O), 1692, 1513, 1369, 1288, 1251, 1035, 830, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 9.2 Hz, Ar**H**), 7.45-7.31 (5H, m, Ar**H**), 6.95 (2H, d, J = 9.2 Hz, Ar**H**), 5.37 (1H, bs, O**H**), 4.00 (1H, d, J = 9.5 Hz, C$\mathbf{H}_2$N), 3.82 (3H, s, OC$\mathbf{H}_3$), 3.56 (1H, d, J = 9.5 Hz, C$\mathbf{H}_2$N), 1.76 (1H, app dq, J = 14.0, 7.5, 7.5, 7.5 Hz, C$\mathbf{H}_2$CH$_3$), 1.44 (3H, s, OC(C$\mathbf{H}_3$)$_2$), 1.40 (3H, s, OC(C$\mathbf{H}_3$)$_2$), 1.10 (3H, s, C$\mathbf{H}_3$), 0.72 (3H, t, J = 7.5 Hz, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 170.6 (C), 167.3 (C), 157.0 (C), 135.3 (C), 132.2 (C), 128.2 (2 x CH), 128.0 (2 x CH), 127.5 (CH), 122.2 (2 x CH), 114.2 (2 x CH), 86.6 (C), 67.8 (C), 59.0 (CH_2), 55.5 (CH_3), 33.8 (CH_2), 25.3 (CH_3), 24.9 (CH_3), 24.3 (CH_3), 7.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{24}H_{29}NO_5$ $[M+H]^+$: 411.2040, found: 411.2041. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (80:20 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 13.9 min, t_r (major) = 16.2 min.



(3*S*,4*R*)-*tert*-butyl-1-benzyl-4-hydroxy-4-methyl-2-oxo-3-phenylpyrrolidine-3-carboxylate (223c). The title compound was prepared according to general procedure U from precursor **222c** and isolated as a white solid. m.p. 162-163 °C; IR ($CHCl_3$) 3434 (OH), 1743 (C=O), 1684, 1457, 1368, 1267, 1158, 841, 748, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.28 (10H, m, Ar**H**), 5.16 (1H, bs, O**H**), 4.78 (1H, d, J = 14.6 Hz, C$\mathbf{H}_2$Ph), 4.47 (1H, d, J = 14.6 Hz, C$\mathbf{H}_2$Ph), 3.42 (1H, d, J = 9.6 Hz, C$\mathbf{H}_2$N), 3.04 (1H, d, J = 9.6 Hz, C$\mathbf{H}_2$N), 1.42 (9H, s, OC(C$\mathbf{H}_3$)$_3$), 0.91 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR (69.2 MHz, $CDCl_3$) δ 170.7 (C), 168.4 (C), 135.9 (C), 135.0 (C), 128.7 (2 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.0 (2 x CH), 127.8 (2 x CH), 127.4 (C), 83.9 (C), 66.9 (C), 57.3 (CH_3), 47.1 (CH_2), 27.7 (3 x CH_3), 24.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{23}H_{27}NO_4$ $[M+H]^+$: 381.1935, found: 381.1935. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (minor) = 7.3 min, t_r (major) = 7.7 min.

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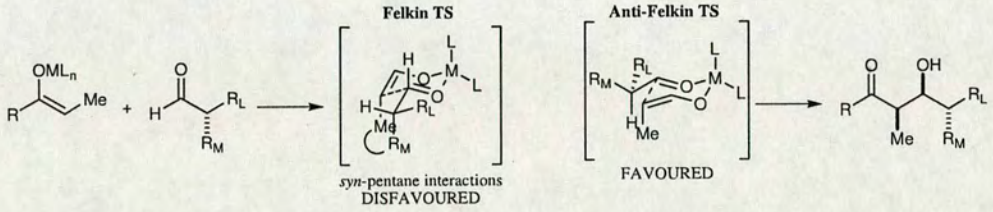
Appendix 1

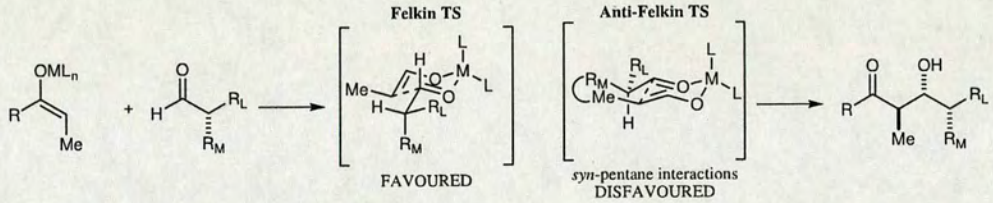
Felkin Control

The attack of an enolate to an aldehyde bearing an α-stereocentre often leads to excellent stereocontrol.[1]

Transition states for Z(O)-Enolate Aldol Reactions



Transition states for E(O)-Enolate Aldol Reactions



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Appendix 2

Publications in support of thesis.

1. **Diastereoselective Synthesis Of 4-hydroxypiperidin-2-ones via Cu(I)-Catalysed Reductive Aldol Cyclisation,** Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.

2. **Diastereoselective Cobalt-Catalysed Reductive Aldol Cyclisations Using Diethylzinc As The Stoichiometric Reductant,** Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729.

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Diastereoselective Synthesis of 4-Hydroxypiperidin-2-ones via Cu(I)-Catalyzed Reductive Aldol Cyclization†

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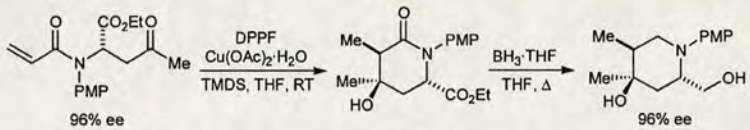
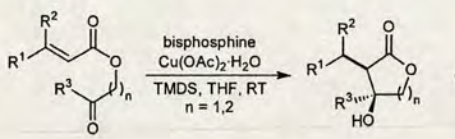
ABSTRACT



4-Hydroxypiperidin-2-ones may be prepared in highly diastereoselective fashion using a Cu(I)-catalyzed reductive aldol cyclization of α,β-unsaturated amides with ketones. Used in combination with proline-catalyzed asymmetric Mannich reactions, this methodology enables the enantioselective synthesis of more highly functionalized piperidin-2-ones and hydroxylated piperidines.

Metal-mediated cyclization reactions provide the basis for many powerful methods of carbocyclic and heterocyclic ring construction.[1] Within this field, intramolecular reductive aldol[2] and Michael[2c,h,3] reactions have proven to be of high utility. These processes are initiated by the hydrometalation of an α,β-unsaturated carbonyl compound, allowing the regioselective generation of a metal enolate under mild reaction conditions. Subsequent intramolecular trapping of the enolate with an appropriate electrophile leads to the cyclic product, often with high levels of diastereoselectivity. The majority of such processes reported thus far have been concerned with the preparation of carbocycles; however, we recently reported a copper(I)-bisphosphine catalyzed reductive aldol cyclization (eq 1) that affords a variety of five-



(1)

and six-membered β-hydroxylactones in moderate to good yields and with moderate enantioselectivites when suitable chiral bisphosphines are employed.[4] Herein we describe the extension of this process to the synthesis of 4-hydroxypiperidin-2-ones through the use of the corresponding substrates containing an amide linkage in place of an ester.

† Dedicated to Prof. David A. Evans on the occasion of his 65th birthday.

(1) For representative examples, see: (a) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2964. (c) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−393. (d) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635−662.

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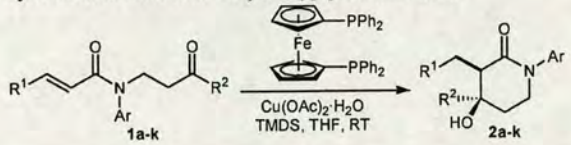
Table 1. Catalytic Reductive Aldol Cyclizations To Form 4-Hydroxypiperidin-2-ones[a]

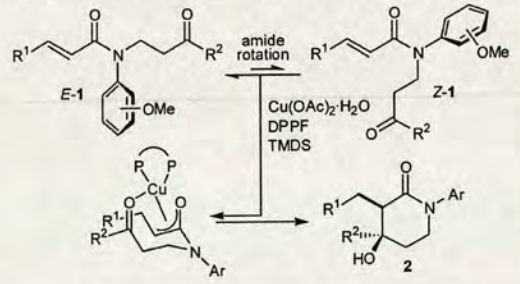


entry	substrate		product		time (h)	yield (%)[b]
1		R = Me **1a**		**2a**	2.5	66
2		R = Et **1b**		**2b**	5.5	61
3		R = *i*-Bu **1c**		**2c**	24	64
4[c]		R = Ph **1d**		**2d**	21	69
5		R = 4-MeC$_6$H$_4$ **1e**		**2e**	24	64
6		R = 2-furyl **1f**		**2f**	24	53
7[c]		R = Me **1g**		**2g**	22	55
8		R = Et **1h**		**2h**	24	52
9		**1i**		**2i**	4	70
10		R = Me **1j**		**2j**	24	70
11[d]		R = Ph **1k**		**2k**	23	65

[a] Reactions were conducted using 1.0 mmol of substrate, 5 mol % Cu, 5 mol % DPPF, and 1.0 mmol of TMDS in 5 mL of THF. [b] Isolated yield. [c] Conducted using 0.2 mL of substrate, 5 mol % Cu, 5 mol % DPPF, and 0.2 mmol of TMDS in 2 mL of THF. [d] $(EtO)_2MeSiH$ (2.0 mmol) was employed in place of TMDS. PMP = *p*-methoxyphenyl, OMP = *o*-methoxyphenyl.

To increase the synthetic versatility of the products, we elected to examine the reactions of substrates **1** containing a removal nitrogen substituent, and PMP (*p*-methoxyphenyl) and OMP (*o*-methoxyphenyl) groups were chosen for this study.[5] *N*-Alkyl-*N*-arylamides such as **1** are known to exist predominantly as the *E*-amide rotamer, with the aryl group twisted such that the plane of the aromatic ring is approximately perpendicular to that of the amide group (Scheme 1).[6] At the outset of these investigations, it was not clear whether this rotamer distribution would have any impact on the ability of these substrates to undergo cyclization.

Scheme 1. Rotational Isomers of Cyclization Precursors **1**



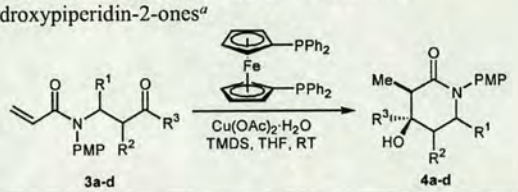
In the event, using the conditions described previously for the corresponding ester substrates[4] (5 mol % $Cu(OAc)_2·H_2O$, 5 mol % 1,1′-bis(diphenylphosphino)-ferrocene (DPPF), and 1 equiv of 1,1,3,3-tetramethylhydrosiloxane (TMDS) in THF at room temperature), a range of substrates **1a**−**k** underwent cyclization to form 4-hydroxypiperidin-2-ones **2a**−**k** (Table 1). The reaction proved to be tolerant to wide variation in the ketone component, with alkyl (entries 1−3 and 7−10), aromatic (entries 4, 5, and 11), and heteroaromatic (entry 6) ketones reacting readily. However, the reaction was less tolerant of substitution in the α,β-unsaturated carbonyl component. Acryloyl amides were found to be the best substrates, giving the desired piperidin-2-one products for all cases examined (entries 1−6 and 9). Although crotonoyl amides also underwent cyclization (entries 7, 8, 10, and 11), reaction rates and conversions were generally lower.[7] In the case of substrate **1k**, use of $(EtO)_2MeSiH$ in place of TMDS proved to be beneficial (entry 11). The reactions

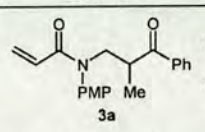
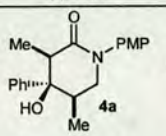
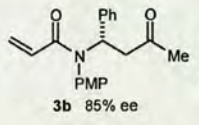
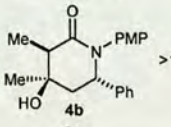
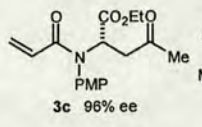
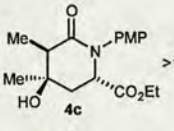
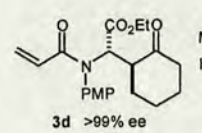
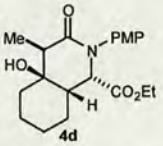
(5) PMP and OMP groups may be removed oxidatively, for example, using ceric ammonium nitrate (CAN). See: (a) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765−2768. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153−7154. For the removal of OMP groups using $PhI(OAc)_2$, see: (c) Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410.

(6) (a) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965**, *6*, 2995−3001. (b) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177−6180. (c) Curran, D. P.; Hale, G. R.; Geib, S. J.; Balog, A.; Cass, Q. B.; Degani, A. L. G.; Hernandes, M. Z.; Freitas, L. C. G. *Tetrahedron: Asymmetry* **1997**, *8*, 3955−3975.

(7) As the size of the substituent on the α,β-unsaturated amide is increased further, the formation of uncyclized side products resulting from both ketone reduction and conjugate reduction also becomes problematic.

Table 2. Formation of C5- and C6−Substituted 4-Hydroxypiperidin-2-ones[a]



entry	substrate	product	dr[b]	yield (%)[c]
1	 **3a**	 **4a**	8:1	78
2	 **3b** 85% ee	 **4b**	>19:1	65
3	 **3c** 96% ee	 **4c**	>16:1	68
4	 **3d** >99% ee	 **4d**	5:1	66

[a] Reactions were conducted using 0.2 mmol of substrate, 5 mol % Cu, 5 mol % DPPF, and 0.2 mmol of TMDS in 2 mL of THF for 2−24 h. [b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Minor diastereomers (not shown) are assumed to possess inverted configurations at C3 and C4. [c] Isolated yield of major diastereomer.

proceeded with high diastereoselectivities (>95:5 by ^{1}H NMR analysis), and the relative configurations of the products[8] were found to match those of the lactone products described previously.[4]

We next examined the effect of preexisting stereocenters in the tether linking the amide and the ketone on the diastereoselectivity of the process (Table 2). Acrylamide **3a**, containing a methyl substituent α to the ketone, cyclized to give a mixture of two diastereomers in a ratio of 8:1, from which piperidinone **4a** was isolated in 78% yield (entry1). By employing L-proline-catalyzed direct asymmetric Mannich reactions to prepare the requisite β-aminoketones,[9] we were able to access acrylamides **3b**−**3d** in enantiomerically enriched form, and these cyclized to give piperidinones **4b**−**4d**, respectively, as the major products (entries 2−4).[10] The

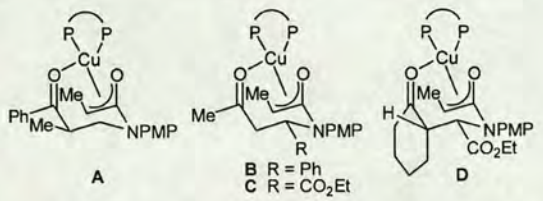
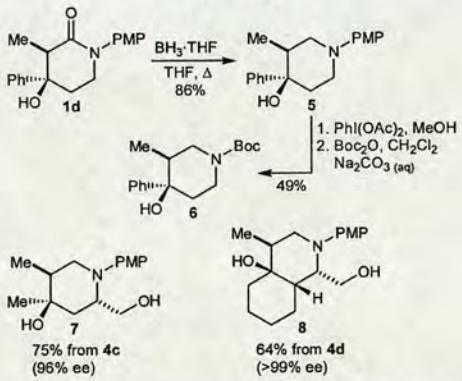


Figure 1. Possible reactive conformations for the cyclization of substrates **3a**−**d**.

moderate to excellent levels of 1,2- and 1,3-asymmetric induction in these reactions may be rationalized by invoking the chelated chairlike conformations **A**−**D** shown in Figure 1, with substituents in the tether linking the amide enolate and the ketone preferring to adopt pseudoequatorial positions.[11]

The synthetic utility of the piperidinone products was illustrated by a number of transformations. Reductive removal of the carbonyl group allows entry to the piperidine ring system, a ubiquitous structural feature of many natural products and biologically important compounds.[12] For example, treatment of **1d** with borane at reflux provided piperidine **5** in good yield, which could be converted into **6** by oxidative removal of the PMP group[5c] followed by in situ treatment of the resulting amine with Boc_2O (Scheme 2). The amide reduction of piperidin-2-ones **4c** and **4d** with

Scheme 2. Conversion of Piperidinone Products into Piperidines



borane was accompanied by reduction of the ethyl esters to give piperidines **7** and **8**, respectively. Polyhydroxylated piperidines are of considerable biological interest due to their potential to act as glycosidase inhibitors.[13]

(8) The relative configurations of the piperidinones **2a**, **2d**, and **2g** were confirmed by X-ray crystallography. See Supporting Information for details. The stereochemistries of the remaining products were assigned by analogy.

(9) (a) Notz, W.; Watanabe, S.-I.; Chowdari, N. S.; Zhong, G.; Betancort, J. M.; Tanaka, J.; Barbas, C. F., III. *Adv. Synth. Catal.* **2004**, *346*, 1131−1140. See also: (b) List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827−833. (c) List, B. *J. Am. Chem. Soc.* **2000**, *122*, 9336−9337.

(10) The stereochemistries of the piperidinones **4a**, **4c**, and **4d** were determined by X-ray crystallography. Analysis of ^{1}H NMR coupling constants was used to establish the stereochemistry of **4b**. See Supporting Information for details.

(11) For related cyclizations involving the SmI_2-promoted intramolecular Reformatsky reactions of β-haloacetoxyketones and an excellent discussion of the factors determining the stereochemical outcomes, see: Molander, G. A.; Etter, J. B.; Harring, L. S.; Thorel, P.-J. *J. Am. Chem. Soc.* **1991**, *113*, 8036−8045.

(12) For reviews of piperidine synthesis, see: (a) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953−2989. (b) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781−1813.

In summary, we have applied copper(I)-catalyzed reductive aldol cyclizations to the highly diastereoselective synthesis of 4-hydroxypiperidin-2-ones. L-Proline-catalyzed Mannich reactions may be used to prepare more highly substituted cyclization precursors in enantiomerically enriched form, enabling the enantioselective synthesis of piperidin-2-ones and piperidines. Current work is focused on identifying catalyst systems that allow a greater range of substituted α,β-unsaturated amides to become viable substrates, developing enantioselective variants of this process, and applying this methodology to other substrate classes. The results from these studies will be reported in due course.

(13) For a recent review, see: Pearson, M. S. W.; Mathé-Allainmat, M.; Fargeas, V.; Lebreton, J. *Eur. J. Org. Chem.* **2005**, 2159−2191.

Acknowledgment. This work was supported by the University of Edinburgh, the Nuffield Foundation (NAL/00827/G), and the Royal Society (2004/R1). AstraZeneca and Merck Sharp & Dohme are gratefully acknowledged for generous unrestricted research funding. The EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea is thanked for their assistance.

Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Diastereoselective Cobalt-Catalyzed Reductive Aldol Cyclizations Using Diethylzinc as the Stoichiometric Reductant

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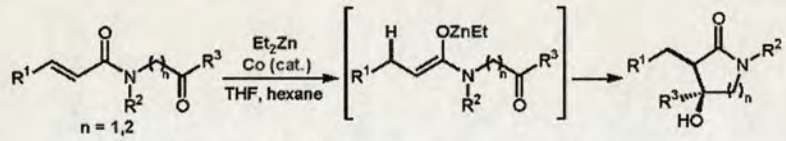
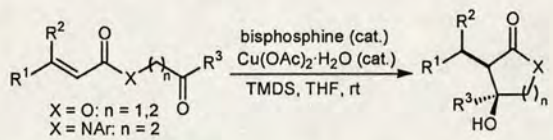
ABSTRACT



Cobalt catalysis enables a new method for the generation of zinc enolates using diethylzinc to reduce α,β-unsaturated amides. This method has been applied to a high-yielding diastereoselective reductive aldol cyclization.

The trapping of aldehydes and ketones with enolates generated in situ via metal-catalyzed conjugate reduction of α,β-unsaturated carbonyl compounds has emerged as a powerful method for accessing aldol products.[1] Despite the tremendous progress that has been made in this area,[1] the continued development of new methods that exhibit high stereocontrol for an increased range of substrates remains an important goal. Recent contributions to this field from our laboratory have detailed copper(I)-bisphosphine-catalyzed reductive aldol cyclizations using TMDS (1,1,3,3-tetramethylhydrosiloxane) as the stoichiometric reductant that could be applied to the synthesis of β-hydroxylactones[2a] and β-hydroxylactams[2b] (eq 1).



(1)

Although the products were obtained with generally high levels of diastereoselectivity (and with moderate enantioselectivities[3] in the case of β-hydroxylactones when suitable chiral bisphosphines were employed[2a]), the process suffered from a number of limitations. First, the yields of these reactions were moderate at best (typically in the range 60−70%) due to competing side reactions.[2] Second, the attenuated electrophilicity of α,β-unsaturated amides compared with the corresponding esters meant that productive cyclizations were limited to those amide substrates where $R^1 = H$

† University of Edinburgh.
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(1) For a seminal reference, see: (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809−4812. For an extensive collection of reports of catalytic reductive aldol reactions, see references cited within: (b) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519−522. For relevant reviews, see: (c) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953−3958. (d) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653−661. (e) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12−21. (f) Chiu, P. *Synthesis* **2004**, 2210−2215. (g) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135−142.

(2) (a) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225−4228. (b) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743−5746.

(3) For enantioselective copper-catalyzed intermolecular reductive aldol reactions with ketones, see: (a) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292−1597. (b) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *46*, 1403−1407.

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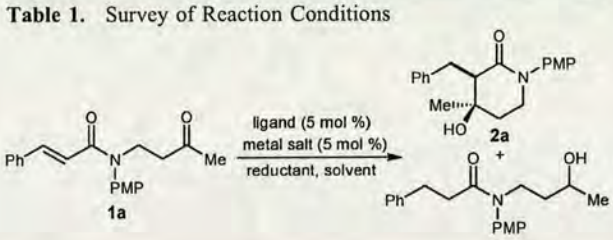
or Me (with R^2 = H).[2b] Therefore, a search for improved reaction conditions was initiated, and we describe herein a new cobalt-based catalyst system that exhibits broader scope for amide-tethered substrates and allows products to be isolated with higher yields.

Initial investigations began with the cyclization of cinnamic amide **1a** (Table 1). Application of our previously

Table 1. Survey of Reaction Conditions



entry	reagents	solvent	temp (°C)	conv (%)[a]	2a/3[a]
1	$Cu(OAc)_2{\cdot}H_2O$, DPPF, TMDS (1 equiv)	THF	rt	77	34:66
2	$Cu(OAc)_2{\cdot}H_2O$, *rac*-BINAP, TMDS (1 equiv)	THF	rt	87	39:61
3	$Cu(OAc)_2{\cdot}H_2O$, DPPF, $PhSiH_3$ (1 equiv)	THF	rt	<5	na
4	$Co(dpm)_2$, $PhSiH_3$ (1 equiv)	CH_2Cl_2	rt	ca. 90	na[b]
5	$Co(dpm)_2$, $PhSiH_3$ (1 equiv)	DCE	rt to 50	ca. 80	na[b]
6	$Co(acac)_2{\cdot}2H_2O$, Et_3B (2 equiv)	THF/ hexane	0 to rt	<5	na
7	$Co(acac)_2{\cdot}2H_2O$, Et_2Zn (2 equiv)	THF/ hexane	0 to rt	>95	>95:5[c]

[a] Determined by ^1H NMR analysis of the unpurified reaction mixture. [b] A complex mixture containing unidentified side products was obtained, with only a trace (<10%) of **2a** present. [c] Product **2a** was isolated in 89% yield. PMP = *para*-methoxyphenyl, DPPF = 1,1′-bis(diphenylphosphino)-ferrocene, TMDS = 1,1,3,3-tetramethylhydrosiloxane, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, dpm = dipivaloylmethane, acac = acetonylacetonate.

reported copper conditions[2] proved ineffective, providing the desired product **2a** but contaminated with significant quantities of the uncyclized side product **3** along with the starting material (entry 1). The formation of **3** may be attributed to conjugate reduction of the α,β-unsaturated amide being slow, allowing prior reduction of the ketone to become competitive. Replacement of DPPF with *rac*-BINAP led to a similar result (entry 2), whereas use of $PhSiH_3$ in place of TMDS led to minimal reaction (entry 3). Having obtained no success with copper-based catalyst systems, our attention turned to the use of other metals. In conjunction with an appropriate chiral ligand, the combination of $CoCl_2$ and $NaBH_4$ has proven useful for the asymmetric conjugate reduction of α,β-unsaturated amides.[4] Unsurprisingly, conditions employing $NaBH_4$ led to rapid reduction of the ketone of **1a**. Conditions employing cobalt salts that were developed for intermolecular reductive aldol reactions[5a] and later extended to aldol cyclizations[5b,c] also proved ineffective, providing complex mixtures (entries 4 and 5). In light of recent reports of organometallic reagents with β-hydrogen-containing alkyl groups being utilized as stoichiometric reductants for a variety of transition-metal-catalyzed reductive couplings,[6] we examined Et_3B[6b−e] and Et_2Zn[6a,b] in our reaction. In the presence of 5 mol % of $Co(acac)_2$ hydrate (degree of hydration ~ 2), Et_3B resulted in no reaction (entry 6), but we were delighted to observe that the more reactive Et_2Zn led to the formation of **2a** in 89% yield with none of the side product **3** being observed (entry 7). No reaction occurs in the absence of $Co(acac)_2{\cdot}2H_2O$.

With effective conditions identified, the scope of the process was next explored (Table 2). Substrates containing a wide range of substitution at both the α,β-unsaturated amide and the ketone[7] underwent cyclization to give 4-hydroxypiperidin-2-one products in generally excellent yields and high diastereoselectivities[8] (entries 1−12). It should be noted that the copper conditions (as in Table 1, entry 1) proved ineffective in the majority of these examples. In a number of reactions, incomplete conversions were observed using $Co(acac)_2{\cdot}2H_2O$ (method A), but the combination of $CoCl_2$ and the electron-rich phosphine Cy_2PPh (method B) was found to provide good results in these cases (entries 10−12). The reaction could also be applied to the formation of pyrrolidin-2-ones (entries 13−15), though with somewhat lower yields and diastereoselectivities. Although 5 mol % of the cobalt source was employed for convenience in these experiments, the reaction is tolerant of lower catalyst loadings. For example, on a 5 mmol scale, substrate **1a** underwent cyclization using 0.5 mol % of $Co(acac)_2{\cdot}2H_2O$ to provide **2a** in 79% yield (entry 2).

Difficulties were encountered when substrates **4a,b** containing phenyl ketones were employed; in contrast to methyl ketones **1l−n** (Table 2, entries 13−15), the desired pyrrolidin-2-ones were obtained in <20% yield along with numerous other side products. However, replacement of Et_2-

(4) (a) v. Matt, P.; Pfaltz, A. *Tetrahedron: Asymmetry* **1991**, *2*, 691−700. (b) Gieger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249−254. (c) Yamada, T.; Ohtsuka, Y.; Ikeno, T. *Chem. Lett.* **1998**, 1129−1130. (d) Ohtsuka, Y.; Ikeno, T.; Yamada, T. *Tetrahedron: Asymmetry* **2003**, *14*, 967−970.

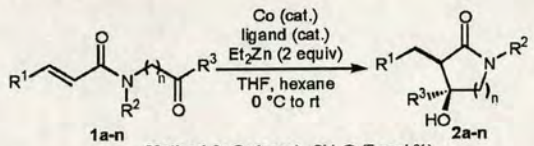
(5) (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005−2008. (b) Baik, T.-G.; Luis, A.-L. Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112−5113. (c) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448−9453.

(6) For selected examples, see: (a) Kimura, M.; Miyachi, A.; Kojima, K.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2004**, *126*, 14360−14361. (b) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033−4034. (c) Molinaro, C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *44*, 129−132. (d) Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 8076−8077. (e) Miller, K. M.; Huang, W.-S.; Jamison, T. F. *J. Am. Chem. Soc.* **2003**, *125*, 3442−3443. For a review, see: (f) Montgomery, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908.

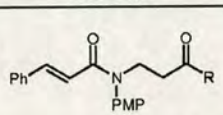
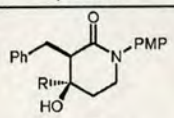
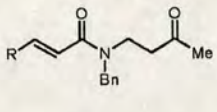
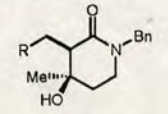
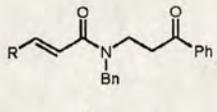
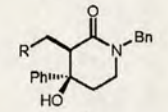
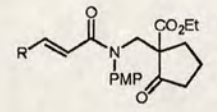
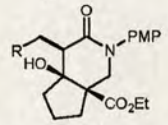
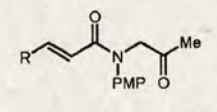
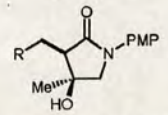
(7) Aldehydes do not serve as competent electrophiles under these conditions, as they undergo reduction and ethylation instead.

(8) The relative stereochemistries of **2f**, **2i**, and **2m** were confirmed by X-ray crystallography and matched those of products obtained previously using copper catalysis (see ref 2). The stereochemistries of the remaining products were assigned by analogy. See Supporting Information for further details.

Table 2. Cobalt-Catalyzed Reductive Aldol Cyclizations[a]

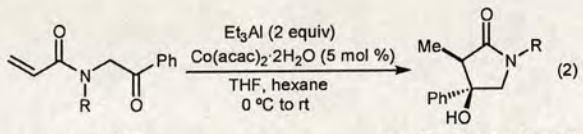


Method A: $Co(acac)_2 \cdot 2H_2O$ (5 mol %)
Method B: $CoCl_2$ (5 mol %), Cy_2PPh (5.5 mol %)

entry	substrate		method	product		dr[b]	yield (%)[c]
1		R = Me **1a**	A		**2a**	12:1	89
2		R = Me **1a**	–[d]		**2a**	12:1	79
3		R = Et **1b**	A		**2b**	9:1	88
4		R = H **1c**	A		**2c**	9:1	88
5		R = *i*-Pr **1d**	A		**2d**	>19:1	>99
6		R = Ph **1e**	A		**2e**	>19:1	97
7		R = 2-furyl **1f**	A		**2f**	>19:1	>99
8		R = Me **1g**	A		**2g**	>19:1	94
9		R = *i*-Bu **1h**	A		**2h**	>19:1	94
10		R = H **1i**	B		**2i**	9:1[e]	56
11		R = Me **1j**	B		**2j**	>19:1[e]	80
12		R = Ph **1k**	B		**2k**	>19:1[e]	88
13		R = H **1l**	A		**2l**	9:1	47
14		R = Ph **1m**	A		**2m**	8:1	56
15		R = OMP **1n**	B		**2n**	14:1	74

[a] Unless otherwise stated, reactions were conducted using 0.2 mmol of substrate in THF (1.5 mL) and hexane (0.4 mL) for 1−24 h. [b] Determined by ^1H NMR analysis of the unpurified reaction mixtures. [c] Isolated yield of the major diastereomer. [d] Reaction conducted using 5 mmol of **1a** using 0.5 mol % of $Co(acac)_2 \cdot 2H_2O$ in THF (10 mL) and hexane (10 mL). [e] Here, dr = (major isomer):(Σ other isomers). OMP = *ortho*-methoxyphenyl.

Zn with Et_3Al allowed isolation of **5a,b** in modest yield (eq 2).[9] Analogues of **4a,b** containing substituted α,β-unsaturated

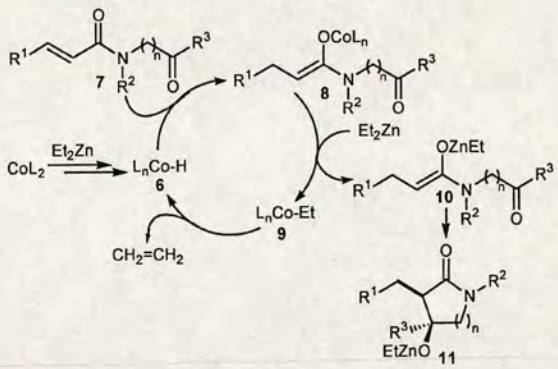


(2)

amides did not cyclize under any conditions examined.

In the absence of detailed studies, discussion of the mechanism of the reaction can only be speculative at this stage. We believe that a zinc enolate is the species that undergoes aldol cyclization, but the precise details leading to the formation of this enolate are not known. One possible catalytic cycle is presented in Scheme 1. Treatment of $Co(acac)_2 \cdot 2H_2O$ (or $CoCl_2$) with Et_2Zn results in the formation of a cobalt hydride species **6**,[10] presumably via a transmetalation/β-hydride elimination sequence. Hydrometalation of

Scheme 1. Plausible Catalytic Cycle

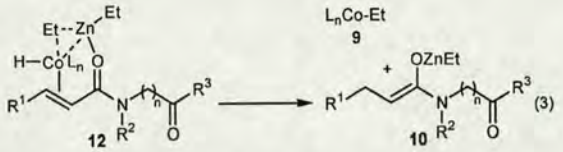


the substrate **7** with **6** generates a cobalt enolate **8**[11] that reacts with Et_2Zn to give an ethylzinc enolate **10**[11,12] and an ethylcobalt species **9**. Enolate **10** then undergoes cyclization to give the zinc alkoxide **11**, whereas the ethylcobalt species **9** undergoes β-hydride elimination to regenerate **6** along with ethylene. This mechanism bears similarities to those proposed for catalytic variants of the Reformatsky reaction employing

(9) Pyrrolidin-2-ones **5a,b** were accompanied by ca. 15% of the corresponding products resulting from conjugate addition of an ethyl group from Et_3Al followed by aldol cyclization.

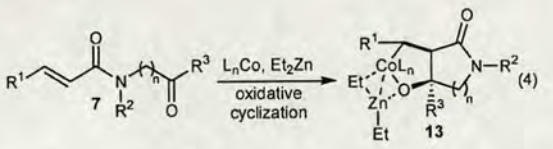
α-bromocarbonyl compounds and dialkylzinc reagents mediated by rhodium[13a] and nickel.[13b,c]

Another scenario that we do not rule out involves the participation of Et_2Zn at an earlier stage of the mechanism. Binding of Et_2Zn to the α,β-unsaturated carbonyl in Lewis acidic fashion, along with Lewis basic interaction with the cobalt hydride via three-center, two-electron bridging of a zinc−ethyl bond (as in **12**, eq 3), would lead to zinc enolate **10** without the intermediacy of a cobalt enolate. Although

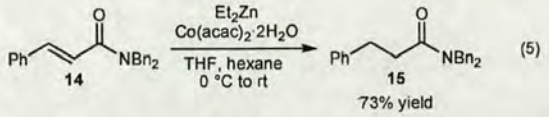


to our knowledge this type of bridging interaction has not been invoked for a cobalt-catalyzed reaction, it has been proposed for a number of related Ni(0)-catalyzed alkylative couplings to explain the accelerating effect of organozinc reagents.[14a,b] Furthermore, it has been observed crystallographically for cobalt[14c] and nickel[14d,e] complexes involving Grignard[14c,d] and organoaluminum[14e] reagents.

Yet another possibility that was initially considered involves the Et_2Zn-assisted oxidative cyclization[14a] of a low-valent cobalt species with substrate **7** to form the cobaltacycle **13** (eq 4).



Metallacycles have been implicated as intermediates in a number of cobalt-[15] and nickel-catalyzed[6f] reductive couplings; in the present case, the final product would be formed from **13** by a sequence involving transmetalation, β-hydride elimination, and reductive elimination. However, a number of observations led us to conclude that this pathway is not operative. First, reaction in the presence of catalytic quantities of a variety of chiral ligands[16] led to racemic products in all cases, providing circumstantial evidence that cobalt is not involved in the stereochemical-determining step. Second, the simple α,β-unsaturated amide **14** underwent conjugate reduction to give **15** in 73% yield under these conditions (eq 5), demonstrating that a second electrophilic π-component is not required for the reaction to proceed.



In conclusion, we have developed an efficient and highly diastereoselective cobalt-catalyzed reductive aldol cyclization that utilizes Et_2Zn as the stoichiometric reductant. This study has highlighted two important features: (i) conjugate reduction of α,β-unsaturated amides using Et_2Zn, which to our knowledge has not been developed as a general synthetic method,[17] and (ii) a mild new approach to access zinc enolates that does not require the prior formation of an alkali metal enolate (for transmetalation with a zinc halide) or the use of α-halocarbonyl compounds (which can be difficult to prepare for complex substrates). We anticipate this method of zinc enolate generation will find application in a range of other reactions. Further studies in this area will be reported in due course.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The oxidation state of cobalt species **8** is not known, though we assume a reduction occurs to generate a low-valent cobalt hydride. For the presumed generation of cobalt hydride by treatment of $Co(acac)_3$ with Et_2AlCl, see: Takacs, J. M.; Mehrman, S. J. *Tetrahedron Lett.* **1996**, *37*, 2749−2752.

(11) Although we have arbitrarily depicted enolates as being O-bound, high C-bound character is possible.

(12) For a discussion of the preparation, characterization, and reactivity of an ethylzinc enolate, see: Hansen, M. M.; Bartlett, P. A.; Heathcock, C. H. *Organometallics* **1987**, *6*, 2069−2074.

(13) (a) Kanai, K.; Wakabayashi, H.; Honda, T. *Org. Lett.* **2000**, *2*, 2549−2551. (b) Adrian, J. C., Jr.; Snapper, M. L. *J. Org. Chem.* **2003**, *68*, 2143−2150. (c) Cozzi, P. G.; Rivalta, E. *Angew. Chem., Int. Ed.* **2005**, *44*, 3600−3603.

(14) (a) Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636−4646. (b) Subbaraj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 11210−11211. (c) Jonas, K.; Koepe, G.; Krueger, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 923−925. (d) Kaschube, W.; Pörschke, K.-R.; Angermund, K.; Krüger, C.; Wilke, G. *Chem. Ber.* **1988**, *121*, 1921−1929. (e) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810−12811.

(15) (a) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696−9697. (b) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6203−6206.

(16) Ligands screened included chiral diols, bisoxazolines, bis(oxazolinyl)pyridines, semicorrins, and bisphosphines.

(17) For an isolated example of conjugate reduction of a sterically hindered enone using Et_2Zn under nickel catalysis, see: Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205−1215.